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Therapeutic Effectiveness of Interferon-α2b Against COVID-19: The Cuban Experience

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A prospective observational study was conducted for assessing the therapeutic efficacy of interferon (IFN)-α2b in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the first month after the coronavirus disease 2019 (COVID-19) outbreak began in Cuba. From March 11th to April 14th, 814 patients were confirmed SARS-CoV-2 positive in Cuba. Seven hundred sixty-one (93.4%) were treated with a combination of oral antivirals (lopinavir/ritonavir and chloroquine) with intramuscular administration of IFN-α2b (Heberon® Alpha R, Center for Genetic Engineering and Biotechnology, Havana, Cuba), 3 times per week, for 2 weeks. Fifty-three patients received the approved COVID protocol without IFN treatment. The proportion of patients discharged from hospital (without clinical and radiological symptoms and nondetectable virus by real-time polymerase chain reaction) was higher in the IFN-treated compared with the non-IFN treated group (95.4% vs. 26.1%, $P < 0.01$). The case fatality rate (CFR) for all patients was 2.95%, and for those patients who received IFN-α2b the CFR was reduced to 0.92. Intensive care was required for 82 patients (10.1%), 42 (5.5%) had been treated with IFN. This report provides preliminary evidence for the therapeutic effectiveness of IFN-α2b for COVID-19 and suggests that the use of Heberon Alpha R may contribute to complete recovery of patients.

Keywords: interferon, COVID-19, SARS-Cov-2

Introduction

The clinical spectrum of coronavirus disease 2019 (COVID-19) varies from asymptomatic infection to mild symptoms to severe acute respiratory illness and death (Rothan and others 2020). There is an urgent need for antiviral drugs to effectively treat this disease. Owing to their antiviral properties and known mechanisms of action, type I interferons (IFN-α/β) present as candidate broad spectrum antivirals for global virus outbreaks (Wang and Fish 2019). In a recent clinical study, evidence was provided that IFN-α2b treatment accelerated viral clearance from the airways and reduced circulating levels of the inflammatory biomarkers IL-6 and C-reactive protein in COVID-19 cases (Zhou and others 2020a). In previous coronavirus (CoV) epidemics in 2002 by severe acute respiratory syndrome (SARS)-CoV and 2012 by Middle East respiratory syndrome-CoV, evidence was provided that coronaviruses (CoVs) encode in their genome factors that specifically block an IFN response, including preventing the activation of MyD88 associated with IFN production and STAT1, associated with IFN signaling (Wang and Fish 2019). Notably, for both outbreaks, evidence was provided for the antiviral effects of type I IFNs, suggesting that IFN treatment can

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override the inhibitory effects of CoVs (Loutfy and others 2003; Hart and others 2014).

In the absence of a vaccine, a number of candidate antivirals are currently under consideration around the globe (Liu and others 2020). Remdesivir is considered the most promising (Jean and others 2020); it functions by inhibiting the activity of RNA-dependent RNA polymerases (RdRp). Case studies describing the use of remdesivir for COVID-19 have been reported (Holshue and others 2020). Ongoing randomized controlled clinical trials will evaluate the safety and antiviral efficacy of remdesivir in patients with mild to moderate or severe COVID-19 (NCT04292899, NCT04292730, NCT04257656, NCT04252664, and NCT04280705). Favipiravir, an anti-influenza medication that also is an RdRp inhibitor is under investigation for COVID-19, but to date clinical data suggest limited efficacy (Sanders and others 2020). The HIV protease inhibitor lopinavir/ritonavir (LPV/RTV) has seen disappointing outcomes in COVID-19 patients (Cao and others 2020), this despite evidence for LPV/RTV plus ribavirin being effective *in vitro* against SARS-CoV (Chu and others 2004). The antiviral activities of chloroquine (Devaux and others 2020) and hydroxychloroquine (Colson and others 2020) against SARS-CoV-2, prompted further evaluation in clinical studies, where early data suggest that they may contribute to inhibition of pneumonia exacerbation and shortening of disease course (Gao and others 2020).

Guidelines issued by the expert committee of the World Health Organization (WHO) identified IFN-α2b as a potential antiviral for the treatment and prevention of COVID-19 (WHO 2020a). Early on in the outbreak, the Chinese government recommended the use of IFN-α for the treatment of COVID-19 (Qiu and others 2020). Several ongoing clinical studies evaluating IFN-α2b for the treatment of COVID-19 are registered at clinicaltrials.gov (Belhadi and others 2020).

Heberon® Alpha R is a human recombinant IFN-α2b formulation produced by the Center for Genetic Engineering and Biotechnology, Havana, Cuba, with demonstrated antiviral efficacy and a proven safety profile over 34 years (Nodarse-Cuni and Lopez-Saura 2017). Herein, we report the first results of the use of Heberon Alpha R as part of the Cuban protocol (Infomed, Portal of the Cuban Health Network 2020) for the management of COVID-19.

Materials and Methods

Patients and treatments

A multicenter prospective observational study was conducted, which included all patients in Cuba with confirmed SARS-CoV-2 infection during the first 33 days of the epidemic in the country, March 11 to April 14, 2020. Patients were considered COVID-19 positive based on virus detected by real-time polymerase chain reaction (RT-PCR).

Patients with confirmed SARS-CoV-2 infection, who gave informed consent and had no contraindications for IFN treatment described in the product information sheet, received therapy as approved in the Cuban COVID protocol. Namely, a combination of antivirals and intramuscular IFN-α2b human recombinant (Heberon Alpha R) administration. Antivirals used were LPV/RTV (250 mg, 1 capsule b.i.d. (500 mg/day) for 30 days and chloroquine 150 mg, 1 tablet twice a day (300 mg/day) for 10 days. IFN treatment was administered by intramuscular injection 3 million IU 3 times per week, for 2 weeks. To treat pediatric cases, the 3 drugs were adjusted for age and weight or body surface (ie, IFN: 100.000 IU/kg). Patients with contraindications or who did not consent to receive IFN were treated with the Cuban protocol lacking IFN, that is, only LPV/RTV and chloroquine. For those cases whose disease progressed to become severe and critical, requiring intensive care unit (ICU) support, treatment with Heberon Alpha R was stopped.

Addition of Heberon Alpha R to the Cuban protocol was approved by the Cuban National Regulatory Authority, CECMED, which maintained surveillance of the scientific evidence obtained. The protocol of this study was evaluated and approved by a centralized Research Ethics Committee, representing all hospital institutions enrolled in the diagnosis and treatment of patients. This clinical research is registered with the code RPCEC00000318 in the Cuban Public Registry of Clinical Trials (RPCEC 2020).

PCR confirmation of SARS-CoV-2

A qualitative RT-PCR for SARS-CoV-2 was performed. Throat swab specimens from the upper respiratory tract of patients were placed into collection tubes prefilled with 150 μL of virus preservation solution, and total RNA was extracted using commercial kits: LightMix® Modular Sarbecovirus E-gene (Roche), LightMix Modular SARS-COV-2 (COVID19 RDRP-GENE) (Roche), LightMix Modular EAV RNA Extraction Control (Roche), LightCycler Multiplex RNA Virus Master (Roche), QIAamp® Viral RNA MiniKit (250) (Quiagen). RT-PCR positivity was required before the start of treatment. Evolutionary PCR was performed 14 days later (at the end of treatment) and repeated weekly, if necessary, to undetectable values. Samples were designated positive (+) or negative (–).

Hematological and biochemical profiles were assessed at admission and every 72 h using routine clinical laboratory procedures.

Endpoints

The primary endpoint was the proportion of patients discharged from hospital (ie, discharge criteria were according to clinical, radiological, and laboratory evaluations). Clinical criteria: patient in stable condition and afebrile for >3 days, regular breathing and normal respiratory rate, clear conscience, unaffected speech, and normal diet. Radiological criteria: significant improvement without signs of organ dysfunction in lung images. Laboratory criteria: Two consecutive PCR (–) with at least 24 h apart. The secondary endpoint was the case fatality rate, (CFR), defined as the number of confirmed deaths divided by the number of confirmed cases.

Statistical analysis

Descriptive statistics (Table 1 and group means reported in the text) convey the data as is. CFR was adjusted by age, gender, and the presence of comorbidities. Note that age was coded as either a continuous variable or binary variable (with >50 or >60 as the threshold).

The association between qualitative variables was analyzed using contingency tables. For the comparison of proportions,

Table 1. Demographics and Clinical Characteristics of Patient Cohort

	IFN n = *761*	*No IFN* n = *53*	P
Age[a] (years)	42.9 (**2–96**)	66.9 (**1–101**)	<0.01
Male	380 (49.9%)	27 (50.9%)	1.0
Female	381 (50.1%)	26 (49.1%)	1.0
ICU[b]	42 (5.5%)	40 (75.5%)	$<10^{-5}$
Comorbidities[c]	24 (3.2%)	30 (56.6%)	$<10^{-5}$

Bold values represent range.
[a]Median is reported.
[b]Criteria for ICU: required artificial ventilation, acute respiratory distress syndrome.
[c]High blood pressure, diabetes mellitus, ischemic heart disease, chronic kidney failure, asthma, obesity, chronic obstructive pulmonary disease, pancreatic cancer, liver cirrhosis, bladder neoplasia, gastritis, hypothyroidism, glaucoma, myasthenia gravis, HIV.
ICU, intensive care unit; IFN, interferon.

the Fisher's exact test calculator was used. The odds ratio (OR) was applied as a measure of association between treatments and outcomes. The nonparametric Mann–Whitney *U* test was used for comparing independent samples.

Results

The Cuban protocol (Infomed, Portal of the Cuban Health Network 2020) for clinical management of COVID-19 was initiated on March 11, 2020, concomitant with the diagnosis of the first 3 patients in the country. By April 14, according to the Cuban Ministry of Public Health (MINSAP 2020), 814 individuals had been confirmed positive for SARS-CoV-2 infection, 761 of them (93.4%) were treated with the established protocol, including Heberon Alpha R and 53 (6.6%) received the Cuban protocol without IFN.

The virological diagnosis was made in patients with persistent clinical symptoms for 72 h and required 2 consecutive PCR(+) results, at least 24 h apart. All patients who received IFN-α2b started treatment on the fifth day of symptom onset.

Table 1 describes the demographics of all patients included in this study. The average age of all cases was 44.3 years, with a nonsignificant difference between the genders.

Patients who did not receive IFN were older (median 66.9 years vs. 42.9 years) with a higher incidence of comorbidities (56.6% vs. 3.2%), such as high blood pressure, ischemic heart disease, and diabetes mellitus.

On April 14, 639 (78.5%) patients remained hospitalized under protocol care (herein considered as patients with unknown outcome). Of the individuals with known results (Table 2), the highest proportion that became PCR(–) for SARS-CoV-2 and that resolved their disease were those treated with IFN (95.4% vs. 26.1%, $P < 0.01$). According to the OR estimation, an individual treated with Heberon Alpha R had a 58.7 times greater likelihood to achieve recovery.

Table 2. Interferon Treatment Promotes Recovery from COVID-19

Known outcome n = *175*	*IFN* n = *152*	*No IFN* n = *23*	P
Discharged	145 (95.4%)	6 (26.1%)	<0.01
Overall CFR	7 (0.9%)	17 (32.1%)	<0.01
CFR for several/ critical cases	7 (21.9%)	17 (48.6%)	<0.05
Age of deceased[a]	69.3 (49–91)	68.8 (38–101)	0.92

[a]Median is reported.
COVID-19, coronavirus disease 2019; CFR, case fatality rate.

On the cutoff date (April 14, 2020), the overall Cuban CFR was 2.95% (MINSAP 2020). The CFR for patients treated with IFN-α2b was 0.92 ($P < 0.01$). These CFRs are lower than those reported on the same date by the WHO (WHO 2020b): Global CFR = 6.34% and Pan American Health Organization (PAHO 2020) CFR = 4.05% (for the region of the Americas). Clinical, radiological, and virological evaluation revealed that there were more patients not treated with IFN-α2b who had an unfavorable outcome of disease (ie, presence of clinical and pulmonary symptoms and/or detectable virus).

To better address the influence of IFN treatment on CFR, we next considered the clinical status of patients in the context of severity of disease, using admission to ICU as a criterion for severe disease. During the course of treatment, 82 patients (10.1% of all the COVID-19 cases) were admitted to the ICU. Notably, only 42 had been treated with IFN, representing 5.5% of the total number of this treatment cohort in the study. Progression to a severe or critical disease state, characterized by a requirement for artificial ventilation and the presence of acute respiratory distress syndrome occurred in 67 (8.2% of all COVID-19 cases) and the significant difference ($P < 0.05$) between the patient cohorts remained unchanged: there were 35 patients (representing 66.0% of the cases of COVID-19 who had not received IFN treatment) and 32 patients (4.2% who had received IFN treatment).

IFN treatment was withdrawn for those patients who progressed to critical disease. Nevertheless, the effects of IFN treatment on subsequent CFR revealed that prior IFN treatment was associated with a 3.37 times greater likelihood of survival, since those critical patients not treated with IFN (48.6%) did not survive, compared with 21.9% of the IFN-treated patient who survived ($P < 0.05$).

Analysis of fatalities showed that 22 of the 24 (91.7%) were >44.3 years and 19 (79.2%) were >55 years. There were more deaths among men: 16 men compared with 8 women. The estimated CFR in men with comorbidities is higher for individuals above the age of 45 years: 16.5-fold greater likelihood of death.

Irrespective of age, CFRs for those with comorbidities is much higher (87.5% vs. 0.52%). In this patient cohort, 7 (1.8%) of those <45 years of age and 47 (11.4%) older had comorbidities. Twenty-one (38.9%) of individuals with comorbidities died, compared with 3 (0.39%) with no comorbidity. Elderly age and arterial hypertension represented the major risk predictors for death; in patients >55 years, this increased from 4.9% to 38.9%.

The lower incidence of comorbidities in the IFN-treated patients may have contributed to their 4.34-fold greater survival advantage compared with those had not been treated with IFN (Table 1). However, this advantage disappears in the subgroup of 28 patients with high blood pressure. High blood pressure was a comorbidity in 27 (32.9%) of the 82 patients who required intensive care.

After adjusting for cohort characteristics on efficacy endpoint, the IFN-related CFR remained significant regardless of gender ($P = 0.45$). Although the IFN-related CFR

was affected by comorbidities ($P < 0.1 \times 10^{-5}$), these comorbidity effects did not negate or eliminate the difference in CFR between IFN-treated individuals and those not treated with IFN ($P = 0.0241$). To compensate for age differences between the groups, an adjustment was made for age, considering it as a categorical variable (<50 years vs. >50 years; <60 years vs. >60 years). Age was significant as a covariate for CFR (P values ranged 0.1×10^{-4} to 0.1×10^{-5}). The IFN-related CFR was significantly affected by age (P values ranged 0.042 to 0.0003). However, the effects of IFN treatment remain significant regardless of age threshold, compared with those not treated with IFN ($P < 0.1 \times 10^{-5}$).

Discussion

All confirmed patients with COVID-19 in Cuba during the period March 11–April 14, 2020 were included in this study. The demographic distribution of patients included in this study conformed to findings in China (Lai and others 2020), in several European countries (Gebhard and others 2020) and the United States (CDC 2020), reporting mostly a seemingly gender-neutral distribution of the confirmed COVID-19 cases and median age between 40 and 60 years. Older persons with pre-existing hypertension and/or diabetes were more prevalent in our no-IFN treated cohort and this age-related trend of comorbidities was similar to data reported by Zhou and others (2020b).

In this study, the median age was higher in those patients who did not receive IFN. Despite this, data analysis revealed that age was not a variable that negated the effects of IFN treatment. Notably, the CFR of COVID-19 by age was consistent with data from other countries that suggest that the elderly are at greater risk for severe disease and death (Zhou and others 2020b).

To eliminate COVID-19 it is critical to prevent viral transmission. The data extracted from clinical records of all patients in the first month of the epidemic, reveals that the use of Heberon Alpha R improved both the rates of recovery and case fatalities. Our findings support the potential efficacy of human IFN-α2b in suppressing SARS-CoV-2 infection and reducing progression to severe disease.

This study reports on the intramuscular administration for IFN-α2b compared with the earlier published findings of inhaled IFN-α2b (Zhou and others 2020a) or ongoing clinical studies (Belhadi and others 2020). An aerosol administration has the advantage of specifically targeting the respiratory tract; however, the pharmacodynamics and pharmacokinetics of this mode of administration are not known (Sallard and others 2020). In contrast, intramuscular administration is well described for Heberon Alpha R and its safety profile has been extensively studied and shown to be safe in a considerable number of clinical trials (Nodarse-Cuni and Lopez-Saura 2017). After the evidence of our results, the feasibility of intramuscular administration of IFN to achieve therapeutic effect in patients with COVID-19 should be considered. Randomized clinical trials (RCTs) are required to compare both routes of administration.

Data analyses in this study were limited, because the study endpoint outcomes, namely hospital discharge (recovery) and CFR for a large number of the cases remained unknown at the time of study termination. However, the greater proportion of patients recovered after treatment with IFN-α2b should be considered as evidence that the use of this product is beneficial, useful, and effective. The actual proportion of recovered patients may increase, because, of the cohort of 607 hospitalized patients treated with IFN-α2b, there are 599 patients (98.7%) in stable clinical condition not included in the recorded outcomes.

The limitations of this open nonrandomized observational study include unbalanced demographics between treatment arms of unequal size. Nevertheless, the purpose of this study was to rapidly evaluate if inclusion of IFN-α2b at the doses and therapeutic regimen employed, offered a therapeutic benefit to COVID-19 cases. Recent publications suggest that treatment with chloroquine (Devaux and others 2020) or LPV/RTV (Chu and others 2004) may offer little therapeutic benefit in COVID-19. With this information, we postulate that IFN treatment in the regimen employed is likely to be the active antiviral of choice against COVID-19.

Regardless of the identified limitations, this report provides evidence of the effectiveness of IFN-α2b as an antiviral treatment for SARS-CoV-2 infection and suggests that the use of Heberon Alpha R may contribute to recovery from COVID-19. Further studies are needed for additional efficacy and safety profile evaluation of Heberon Alpha R, specifically an RCT for comparison with other potential antivirals.

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Authors' Contributions

D.G., R.V., J.R.B., and R.E.D. were responsible for patient care and treatment; H.B.R., J.C.R., A.P., L.D.R.L., and N.M. made clinical oversight and clinical data collection; R.P. led the working group, analyzed and conducted data analysis, data interpretation, literature searches, and article writing.

Author Disclosure Statement

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