



Safety and efficacy of intranasal recombinant human interferon alfa 2b as prophylaxis for COVID-19 in patients on a hemodialysis program

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Abstract

Introduction: Patients diagnosed with end-stage chronic kidney disease on a hemodialysis program (HDP) represent a risk group for COVID-19. Scientific societies have developed guidelines for the prevention of contagion, but there is no prophylactic medicine in them.

Objectives: To describe the safety and efficacy of recombinant intranasal human Interferon alfa 2b as prophylaxis for COVID-19 in patients in an HDP.

Patients and Methods: Intervention description through the monitoring of 15 patients in outpatient HDP. Prior to the administration of the drug, clinical, radiological evaluation and hematology and blood chemistry studies were performed. Daily contact was made with each study patient in person or by telephone, asking about the occurrence of adverse events or symptoms of disease.

Results: In 47% of the patients, there was leukopenia, lymphopenia in 67% and anemia and thrombocytopenia in 33% respectively, prior to the use of the drug. There was no clinical suspicion of COVID-19 in any of them. Adverse events occurred in 3 patients (20%), all were mild and non-severe. All patients were negative for SARS-CoV-2 real-time polymerase chain reaction (rtPCR) and antibody studies 45 days after the study started.

Conclusion: the use of intranasal recombinant human interferon alfa 2b as prophylaxis of COVID-19 in patients in a HDP at a dose of 1 MIU daily for ten days, as part of a prevention protocol, has an adequate safety profile. None of the patients in the series was infected with SARS-CoV-2 during the surveillance period.

Keywords: Interferon type I, Coronavirus infections, COVID-19, Hemodialysis units hospital, SARS-CoV-2, Renal insufficiency chronic, Prevention & control

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Introduction

The disease which is caused by the new SARS-CoV-2 coronavirus named COVID-19 has risk factors for infection and poor evolution, consist of old age and the presence of comorbidities such as high blood pressure, diabetes mellitus, ischemic heart disease and end-stage chronic kidney disease (1). The common factor among them is vascular damage, specifically the endothelium, which has been found to be a target for SARS-CoV-2 (2).

Patients diagnosed with end-stage chronic kidney disease on hemodialysis program (HDP) represent a particular risk group. A lot of COVID-19 risk factors exist commonly in these patient. Patients on HDP are considered as immunosuppressed patients because of alteration in lymphocyte population and uremic milieu (3). A proinflammatory state has been described in patients on HDP with a higher risk for cardiovascular diseases (4). The behavior of social isolation cannot be

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■ Implication for health policy/practice/research/medical education

The research is of current importance given the global situation that has caused the SARS-CoV-2 pandemic. The article shows the hygienic-epidemiological measures adopted in hemodialysis units in Cuba. In particular, the safety and efficacy of incorporating a drug for preventive purposes are described. Intranasal recombinant human interferon alfa 2b has antiviral properties and its generalization may be useful in the prophylaxis of COVID-19, in patients on hemodialysis programs, which constitute risk groups for infection.

fully complied with, since HDP patients must periodically attend in medical centers where they will share spaces with other patients and healthcare personnel.

Scientific societies and groups of specialties have elaborated action guides for the prevention of contagion, which generally include hygienic-epidemiological measures aimed at patients, health personnel and the hemodialysis room (5-7).

The revision of the prevention guidelines show to medicine for prophylaxis. There are reports of the use of interferon in the form of nasal drops as a preventive tool in viral respiratory diseases (influenza, rhinovirus, coronavirus) with evidence of antiviral and mitigating effects of the symptomatic period (8,9). However, there have been controversies regarding the dose that provides an antiviral effect with certainty in relation to the appearance of adverse events.

Interferons are glycoproteins known as cytokines, molecules that make up the protective defenses of the immune system for the eradication of pathogens. Interferons get their name for their ability to “interfere” with viral replication and have other functions such as activating immune system cells (eg. natural killer

cells and macrophages) and increasing host defenses by regulating antigen presentation through of the major histocompatibility complex (10). Current research results have shown that SARS-CoV-2 can inhibit the physiological secretion of interferon by host cells and therefore creates a terrain of susceptibility to viral infection (11). In the current situation motivated by COVID-19, the use of recombinant intranasal human interferon alfa 2b (rinh-IFNα2b) as prophylaxis of COVID-19 in patients on HDP may be an interesting option to incorporate into the group of prevention measures established by scientific societies.

Objectives

To describe the safety and efficacy of using rinh-IFNα2b as COVID-19 prophylaxis in patients in a HDP.

Patients and Methods

Study design

The drug was applied to 15 patients in the HDP of the Centro de Investigaciones Médico Quirúrgicas.

In-hospital hemodialysis was performed three times a week on an outpatient basis. Table 1 shows the demographic characteristics, associated diseases, and time on dialysis.

Dosage and method of administration of the drug

Presentation: Recombinant intranasal human interferon alfa 2b, 10 million international units (MIU) per milliliter (mL).

Dose: one drop (0.05 mL = 0.5 MIU) in each nostril, once a day, for 10 consecutive days

Active ingredient: Recombinant human IFN alpha-2b, produced in Escherichia Coli at the Centro de Ingeniería Genética y Biotecnología, Havana, Cuba.

Other ingredients: for each mL

Ethylenediaminetetraacetic acid, disodium salt dihydrate, polysorbate 80 (Tween 80), beta cyclodextrin,

Table 1. Demographic characteristics, time on dialysis and personal pathological history of the patients under study

Patient	Gender	Age	HD time (y)	AHT	ACEI/ARA 2	DM	IHD	HCV	COPD	Others
1	Male	63	20	x	x	x	x			
2	Male	50	12	x	x			x	x	Post-transplant lymphoproliferative syndrome
3	Male	60	18	x	x			x		
4	Female	40	2	x				x		
5	Male	74	3	x					x	Multiple myeloma
6	Female	67	8	x						Breast cancer (liver and lung metastases)
7	Male	62	3	x	x					
8	Male	47	3	x	x					Psoriatic arthritis
9	Female	73	2	x		x	x			Gastric neoplasm
10	Male	70	7	x	x		x			Prostate neoplasm
11	Female	54	8	x						Systemic lupus erythematosus
12	Male	75	1	x						Cerebrovascular disease
13	Male	69	1							
14	Male	40	20	x				x		
15	Male	37	13	x				x		Systemic lupus erythematosus

HD: hemodialysis, AHT: arterial hypertension, ACEI: angiotensin converting enzyme inhibitor, ARA: angiotensin receptor antagonist, DM: diabetes mellitus, IHD: ischemic heart disease, HCV: hepatitis C virus, COPD: chronic obstructive pulmonary disease.

high viscosity carboxymethyl cellulose, thiomersal, sodium chloride, sodium dihydrogenphosphate dihydrate, disodium hydrogen phosphate, water for injection.

Information and prior evaluation

Patients received detailed information about the study objectives, characteristics of the drug under evaluation, possible adverse events and behavior to follow, including the immediate report to the researchers.

Each patient under study was questioned to search for symptoms suggestive of disease, including those suspected of COVID-19. Physical examination, hematology, blood chemistry, chest radiology and thoracic ultrasound were conducted.

Security watch period

Daily contact was made with each study patient in person or by telephone, in which patients were questioned regarding the occurrence of adverse events or symptoms of disease. Adverse events (AE) were classified according to grade as: Mild: AE that is well tolerated, does not interfere with daily activities, does not require treatment and does not interrupt administration. Moderate: AE that interferes with daily activities, requires treatment, and does not necessarily require discontinuation of the causative medication. Severe: AE incapacitating work or usual activities, prolongs hospitalization of the patient because it directly threatens his life and requires the suspension of the causative drug and the administration of a specific treatment to counteract it. AEs were classified according to severity as: 1. Not serious, 2. Causes death, 3. Threatens life, 4. Requires hospitalization, or prolongs it, 5. Causes significant disability/ disability, and 6. Causes birth defects

After 48 hours after the end of the administration of the drug, hematology and blood chemistry studies were repeated.

Efficacy monitoring period

Daily contact was made with each study patient in person or by telephone, in which the patients were questioned regarding the occurrence of symptoms suspected of

disease. On day 45 of the study, all patients underwent SARS-CoV-2 real-time polymerase chain reaction (rtPCR) for SARS-CoV-2 through pharyngeal exudate and blood collection for anti-SARS-CoV-2 LUNGENE® (IgM and IgG) and UMELISA® (IgG) rapid kits; [Figure 1](#).

Other prevention actions

The Centro de Investigaciones Médico Quirúrgicas and the Nephrology, Dialysis and Kidney Transplant Service adopted the preventive measures dictated by the Cuban state and the ministry of public health of the republic of Cuba (12). HDP patients and health personnel were questioned about suspected symptoms of COVID-19 and temperature measurement and hand washing with 0.1% sodium hypochlorite solution were performed at the hospital entrance. Facial protectors were added to the individual protection means of the HDP health personnel in addition to the protective glasses ([Figure 1](#)).

All patients wore surgical masks during hemodialysis and travel. At the end of the work session, in addition to conventional cleaning, general disinfection and surface cleaning with 0.5% sodium hypochlorite solution was performed.

Ethical issues

The research conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Centro de Investigaciones Médico Quirúrgicas (Universidad de Ciencias Médicas de La Habana) approved this study. The institutional ethical committee at Centro de Investigaciones Médico Quirúrgicas accepted all study protocols (CEI-Cimeq 2020-011). Accordingly, written informed consent was taken from all participants before any intervention.

Statistical analysis

Statistical evaluation was performed with the Statistical Package for the Social Sciences (SPSS® 20.0) for Microsoft Windows®. The mean as a summary measure of center for the quantitative variables and the standard deviation as a measure of dispersion were estimated, as well as the percentages for the quantitative variables. The comparison

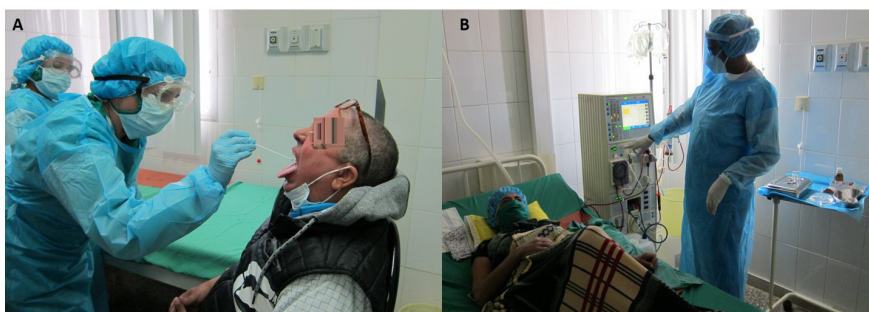


Figure 1. A. Pharyngeal material sampling time for rtPCR SARS-Cov-2, B. Hemodialysis program patient with surgical mask and nurse with n95 respirator, face protector, hat, overcoat and gloves.

Table 2. Hemodialysis related data, nutritional status, and drugs of the patients under study

Patient	Steroids	Statins	Pentoxifylline	Nutritional status	Kt/V	Vascular access	Others
1					>1.4	AVF	
2	10 mg/d			Obese	1 – 1.4	PC	Post-transplant lymphoproliferative syndrome
3				Underweight	> 1.4	AVF	
4	5 mg/d				>1.4	AVF	
5	40 mg/d				>1.4	AVF	Multiple myeloma
6				Malnourished	>1.4	AVF	Breast cancer (liver and lung metastases)
7					>1.4	AVF	
8	5 mg/d	x			>1.4	AVF	Psoriatic arthritis
9		x	x	Obese	>1.4	PC	Gastric neoplasm
10		x			>1.4	AVF	Prostate neoplasm
11	10 mg/d			Underweight	>1.4	AVF	Systemic lupus erythematosus
12		x	x		>1.4	AVF	Cerebrovascular disease
13					>1.4	AVF	
14					>1.4	AVF	
15					>1.4	AVF	Systemic lupus erythematosus

AVF: arteriovenous fistula, PC: permanent catheter.

Table 3. Hematologic variables, coagulation, blood chemistry, markers of inflammation and endothelial dysfunction, prior to medication administration

Patient	WBC (10 ⁹ /L)	Lymphocytes (10 ⁹ /L)	Hemoglobin (10 ⁹ /L)	Platelets (10 ⁹ /L)	D-Dimer (pg/ml)	Fibrinogen (mg/dl)	LDH (mg/dl)	Ferritin (ng/ml)	NLR	PLR
1	3.7	1.2	9.9	145	0.82	182	174	207.0	1.75	120.83
2	8.7	1.3	14.6	174	1.42	200	285	207.0	5.31	133.85
3	3.6	0.8	12.4	276	2.15	200	120	154.1	3.00	345.00
4	6.5	1.5	12.1	170	0.26	193	244	2000.0	2.87	113.33
5	7.2	4.6	12.6	194	0.70	192	219	709.7	0.43	42.17
6	5.8	0.8	8.1	215	0.67	179	262	471.5	5.50	268.75
7	4.4	0.9	10.2	230	0.49	326	255	728.7	3.33	255.56
8	10.6	1.5	12.1	125	1.11	196	246	2000.0	5.53	83.33
9	6.7	1.6	12.0	133	0.57	179	191	918.5	2.75	83.13
10	4.1	0.8	12.1	206	0.17	200	98	2000.0	3.38	257.50
11	3.1	0.7	12.8	57	0.35	192	250	1973.0	3.00	81.43
12	3.9	1.3	10.9	142	0.32	199	270	975.9	1.46	109.23
13	7.7	1.8	13.7	169	1.22	192	239	94.76	2.67	93.89
14	2.9	1.2	10.3	186	0.27	192	199	951.1	1.17	155.00
15	4.5	0.9	12.5	105	1.40	186	205	878.6	3.44	116.67

WBC: White blood cells, LDH: lactic dehydrogenase, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio

of means was carried out by means of the Students' *t* test. Statistical significance was declared when $P < 0.05$.

Results

General characteristics of the study population

The series consisted of 15 patients on a HDP, 11 (73%) male and 4 female (27%). The mean age was 58.7 years of age with age limits of 37-75 years. The mean time on hemodialysis was 8 years, with ranges between 1-20 years. The main comorbidities were hypertension in 14 patients (93%), hepatitis C virus (HCV) infection in 6 patients (40%), neoplastic disease in 5 patients (33%), shown in Table 1.

Hemodialysis was performed with Fresenius® F6 HPS - F10 HPS low flux filters and a polysulfone membrane; except in patient 7, the FX Cordiax high flow filter was used. Table 2 shows the vascular accesses used, Kt/v and other data of interest. Patients received iron dextran intravenously, between 25-100 mg/wk.

Baseline status in relation to hematological variables, coagulation and inflammation markers

In seven patients (47%) there was leukopenia, lymphopenia in 10 (67%), and anemia and thrombocytopenia in five (33%), respectively. Neutrophil-lymphocyte and platelet-lymphocyte rates were found at risk values in three patients (20%) and in one patient (7%) respectively, see Table 3.

Elevated D-Dimer was found in nine patients (60%), see Table 3. There was not any abnormality in serum fibrinogen level, prothrombin time and partial thromboplastin time. LDH was not elevated in any patient and in 11 (73%) patients there was an increase in ferritin, see Table 3.

Baseline physical exam

In nine patients (60%) there was some auscultatory abnormality in the examination of the respiratory system. The oxygen saturation by pulse oximetry was found between 93-100% and the radial pulse between 60-99

beats per minute.

No patient had symptoms and/or signs, nor radiological or ultrasound images suggestive of pneumonia in the course of COVID-19 such as those described in the scientific reports (13,14).

Incidence and characterization of adverse events

Adverse events occurred in 3 patients (20%), all of mild severity and not serious, see Table 4.

Post-intervention status in relation to hematological variables and inflammation markers

Table 5 presents the mean values of a group of laboratory variables at the pre-intervention and post-intervention times.

Viral studies

SARS-CoV-2 rtPCR and COVID-19 antibody studies (IgM and IgG) were negative in all patients.

Discussion

Patients diagnosed with chronic kidney disease in HDP are one of the risk groups for COVID-19.

In the present case series, the high prevalence of comorbidities in patients with chronic kidney disease is demonstrated, finding a higher proportion of hypertension and neoplastic diseases. The finding of lymphopenia is frequent in the study patients, similar to that reported by other authors as characteristics of patients in HDP (3). Similarly, there are some patients with a baseline state characterized by elevation of some inflammation markers (eg. ferritin, LDH) and activation of coagulation [eg. D-dimer] (4).

The baseline characteristics of the patients on HDP, including those that make up the present investigation, complicates the diagnostic suspicion of COVID-19, given that among the prognostic factors for SARS-CoV-2 infection are lymphopenia, elevation of D-Dimer and presence of inflammatory [eg. ferritin, LDH] (15,16).

On the other hand, although some authors have reported that the presentation symptoms of COVID-19 in HDP patients are similar to the patients without renal failure, other authors describe a higher frequency of atypical presentations [eg. digestive symptoms] (16,17).

In this group of patients, surveillance protocols require

an additional alert given the number of variables and confusing situations that can coexist. The possibility of prescribing pharmacological prophylaxis, in addition to hygienic-epidemiological prevention measures, may be useful.

Intranasal use of interferon as prophylaxis for viral respiratory infections has been demonstrated in *in vitro* and *in vivo* studies. In the authors' opinion, the main controversy has been in the dose with antiviral effectiveness and minor adverse events.

The adverse events found in the present study were few, mild, not serious and didn't necessitate drug discontinuation.

When comparing with other articles in the literature, we found that Douglas et al (18) described that the administration of a daily dose of rinh-IFN α 2b of 10 MIU demonstrated antiviral effectiveness, but in a high percentage of participants, it was accompanied by adverse events (nasal irritation, mucosal ulceration, bleeding) that forced the clinical trial to be suspended.

Douglas et al (18), using doses of 2 MIU daily for 28 days, described modest anti-rhinovirus activity and 7.7% of adverse events in the interferon group vs. 0.9% in the placebo group. The main symptoms with this dose were nasal irritation, a dry nose and bleeding that reversed after

Table 5. Comparison of pre- and post-intervention mean values (hematology, coagulation, blood chemistry and inflammation markers)

Variable	Pre-intervention, mean (\pm SD)	Post-intervention, mean (\pm SD)	P
WBC (10 ⁹ /L)	5.6 (2.3)	5.7 (1.9)	0.395
Lymphocytes (10 ⁹ /L)	1.4 (0.9)	1.2 (0.7)	0.115
Neutrophils (10 ⁹ /L)	3.6 (2.0)	3.8 (1.5)	0.345
Hemoglobin (10 ⁹ /L)	11.7 (1.6)	11.5 (1.9)	0.454
Platelets (10 ⁹ /L)	168.5 (54.0)	166.1 (30.2)	0.896
NLR	3.0 (1.5)	3.5 (1.9)	0.045
PLR	150.6 (88.0)	151.4 (47.9)	0.970
Fibrinogen (mg/dL)	200.5 (35.4)	291 (25.7)	0.001
LDH (mg/dL)	212.3 (52.4)	213.6 (62.5)	0.162
Ferritin (ng/mL)	1017.2 (728.9)	991 (623.7)	0.001
APL (UI/L)	386.8 (260.3)	214.6 (157.4)	0.023
GOT (U/L)	23.0 (8.6)	24.4 (11.1)	0.546
GPT (U/L)	26.2 (18.4)	31.8 (18.2)	0.004
GGT (U/L)	78.7 (73.6)	55.1 (53.1)	0.311
Total protein (g/L)	51.7 (5.2)	69.7 (6.5)	0.001
Albumin (g/L)	37.4 (6.4)	41.1 (3.1)	0.076
Uric acid (mmol/L)	406.8 (83.2)	501.6 (89.5)	0.001
Urea (mmol/L)	19.0 (6.0)	26.7 (7.8)	0.001
Creatinine (mmol/L)	870.8 (260.5)	1062.9 (275.8)	0.001
Glycemia (mmol/L)	5.0 (1.2)	4.9 (0.9)	0.791

SD: standard deviation, WBC: White blood cells, NLR: neutrophil - lymphocyte ratio, PLR: platelets - lymphocyte ratio, LDH: lactic dehydrogenase, ALP: alkaline phosphatase, GOT: glutamic oxalacetic transaminase, GPT: glutamic pyruvic transaminase, GGT: gamma glutamyl transpeptidase.

Table 4. Adverse events: type, grade and severity

Patient	Adverse event	Grade	Severity
7	Dry mouth	Mild	Not serious
7	Headache	Mild	Not serious
7	Flu-like syndrome	Mild	Not serious
8	Coryza	Mild	Not serious
11	Coryza	Mild	Not serious
11	Pharyngeal burning	Mild	Not serious

one to two weeks of withdrawing the medication.

Turner et al (19) carried out a study in which they administered rhIFN- α 2b 2 MIU daily for 15 days and compared it with a placebo group. Eight days after the start of the study, all patients were inoculated with nasal solution with coronavirus 229E. In the placebo group 77% developed flu-like symptoms vs 21% in the interferon group, with the duration and severity of the symptoms being shorter in the last group. In relation to the appearance of adverse events (nasal bleeding) this was recorded in 34% in the interferon group vs. 19% in the placebo group. Mucosal ulceration was not observed in any patient, and none of them required withdrawal of the drug.

In the reviewed literature, there is no evidence of adverse effects of the drug in relation to hematological, coagulation or blood chemistry alterations.

With respect to this research, the authors consider that the differences in some results in the laboratory variables monitored post-intervention (eg. creatinine, urea, uric acid) may be related to the time of sample collection with respect to the time of last hemodialysis session. Basal taking was done 24 hours after the last session and post-intervention sample was done 48 hours after the last session.

In the current SARS-CoV-2 pandemic, researchers from the Taihe hospital in Hubei province used intranasal IFN alpha 1b for 28 days in healthcare personnel from areas exposed to the virus. They later compared their results with the situation found in the staff of other Hubei hospitals with new diagnoses of COVID-19. In the interferon group, no personnel was diagnosed with COVID-19, while in the other hospitals, 2,035 patients were diagnosed among the health personnel. There were no described adverse events [except for some cases with slight nasal irritation] (11).

None of the patients included in the present investigation were affected by SARS-CoV-2 infection during a period of more than 45 days under surveillance at times of regional viral circulation in the province with the highest national prevalence. The authors suggest new studies to confirm the effectiveness of the dose used in a similar study population.

Conclusion

The use of intranasal recombinant human interferon alfa 2b as prophylaxis of COVID-19 in patients in a HDP at a dose of 1 MIU daily for ten days, together with a prevention protocol composed of hygienic-epidemiological measures, has an adequate profile of safety in relation to the appearance of few and slight adverse effects. None of the patients in the series was infected with SARS-CoV-2 during the surveillance period.

Limitations of the study

The main limitations of the study consist of the sample size and being a monocentric study. Further studies are needed to confirm the results of the present investigation.

Authors' contribution

AAC, RCG, JTR and JCHP were the principal investigators of the study. AAC, RCG, JTR and JCHP were included in preparing the concept and design. AAC, JTR and JSL revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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None.

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