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

Anselmo Abdo-Cuza1*, Roberto Castellanos-Gutiérrez1, Janete Treto-Ramírez1, Sandra Arencibia-Larin1, Thalía Gómez-Pariente1, Tania González-Fernández1, Julio C. Hernández-Perera1, Katia Ariacha-Stalella1, Niurka Verdecia-Gorrita1, Lisy Vento-Buigues1, Yanet Cordero-Vasallo1, Yusmel Rivero-Yi1, Odalys González-Dias2, Hugo Nodarse-Cuni1, Rafael Machado-Martínez1, Miguel A. Blanco-González1, Julio Valdivia-Arencibia1, Daymiris Mendez-Felipe1, Ernesto Delgado-Almora1, Carlos Gutiérrez-Gutiérrez1, Juliette Suárez-López1, Jorge L. Leiva-Torres1, Alicia Rodríguez-Sotolongo1, Nilda Bejerano-Gil1

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

Citation: Abdo-Cuza A, Castellanos-Gutiérrez R, Treto-Ramírez J, Arencibia-Larin S, Gómez-Pariente T, González-Fernández T, Hernández-Perera JC, Ariacha-Stalella K, Verdecia-Gorrita N, Vento-Buigues L, Cordero-Vasallo Y, Rivero-Yi Y, González-Dias O, Nodarse-Cuni H, Machado-Martínez R, Blanco-González MA, Valdivia-Arencibia J, Mendez-Felipe D, Delgado-Almora E, Gutiérrez-Gutiérrez C, Suárez-López J, Leiva-Torres JL, Rodríguez-Sotolongo A, Bejerano-Gil N. Safety and efficacy of intranasal recombinant human interferon alfa 2b as prophylaxis for COVID-19 in patients on a hemodialysis program. J Renal Endocrinol. 2021;7:e05. doi: 10.34172/jre.2021.05.

Copyright © 2021 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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
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 an 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   | x   |      | Post-transplant lymphoproliferative syndrome |
| 2       | Male   | 50  | 12          | x   | x         | x  | x   |      |      |        |
| 3       | Male   | 60  | 18          | x   | x         |    | x   |      |      |        |
| 4       | Female | 40  | 2           |     |           | x  |      |      |      |        |
| 5       | Male   | 74  | 3           |     |           | x  |      |      |      | Multiple myeloma |
| 6       | Female | 67  | 8           |     |           | x  |      |      |      | Breast cancer (liver and lung metastases) |
| 7       | Male   | 62  | 3           | x   | x         |    |      |      |      | Psoriatic arthritis |
| 8       | Male   | 47  | 3           | x   |           | x  |      |      |      | Gastric neoplasm |
| 9       | Female | 73  | 2           | x   | x         | x  |      |      |      | Prostate neoplasm |
| 10      | Male   | 70  | 7           | x   |           | x  |      |      |      | Systemic lupus erythematosus |
| 11      | Female | 54  | 8           |     |           | x  |      |      |      | Cerebrovascular disease |
| 12      | Male   | 75  | 1           |     |           | x  |      |      |      | Systemic lupus erythematosus |
| 13      | Male   | 69  | 1           |     |           |    |      |      |      | Systemic lupus erythematosus |
| 14      | Male   | 40  | 20          | x   | x         |    |      |      |      |        |
| 15      | Male   | 37  | 13          | x   |           | x  |      |      |      |        |

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 dihydrogen phosphate 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 Medicas 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
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 Cordiaxis 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 \textit{in vitro} and \textit{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-IFNα2b 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 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    |

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

| Variable                        | Pre-intervention, mean (±SD) | Post-intervention, mean (±SD) | P      |
|---------------------------------|------------------------------|-------------------------------|--------|
| WBC (10⁹/L)                     | 5.6 (2.3)                    | 5.7 (1.9)                     | 0.395  |
| Lymphocytes (10⁹/L)             | 1.4 (0.9)                    | 1.2 (0.7)                     | 0.115  |
| Neutrophils (10⁹/L)             | 3.6 (2.0)                    | 3.8 (1.5)                     | 0.345  |
| Hemoglobin (10⁹/L)              | 11.7 (1.6)                   | 11.5 (1.9)                    | 0.454  |
| Platelets (10⁹/L)               | 168.5 (54.0)                 | 166.1 (10.2)                  | 0.896  |
| NLR                             | 3.0 (1.5)                    | 3.5 (1.9)                     | 0.045  |
| PLR                             | 150.6 (68.0)                 | 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)                 | 214.6 (157.4)                 | 0.023  |
| Ferritin (ng/mL)                | 1017.2 (728.9)               | 991 (623.7)                   | 0.001  |
| APL (U/L)                       | 386.8 (260.3)                | 374.6 (207.4)                 | 0.546  |
| GOT (U/L)                       | 23.0 (8.6)                   | 24.4 (11.1)                   | 0.004  |
| GPT (U/L)                       | 26.2 (18.4)                  | 31.8 (18.2)                   | 0.001  |
| 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 (81.2)                 | 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 oxaloacetic transaminase, GPT glutamic pyruvic transaminase, GGT: gamma glutamyl transpeptidase.
one to two weeks of withdrawing the medication.

Turner et al (19) carried out a study in which they administered rininh-IFNα2b 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 later 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 were 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.

Funding/Support
None.

References
1. Wei-jie Guan, Wen-hua Liang, Yi Zhao, Heng-rui Liang, Zhi-sheng Chen, Yi-min Li, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J. 2020;55:2000547. doi: 10.1183/13993003.00547-2020
2. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Is COVID-19 an Endothelial Disease? Clinical and Basic Evidence. Preprints 2020; 2020042024. doi: 10.20944/preprints202004.0204.v1
3. Lepe-Zúñiga JL, Morón-Molina P, García-Nandyaya GA. Caracterización y correlación clínica de la linfopenia en la enfermedad renal en estadio terminal. Rev Med Inst Mex Seg Soc. 2016;54(4):446-53.
4. Baragetti I, El Essawy B, Fiorina P. Targeting Immunity in End-Stage Renal Disease. Am J Nephrol. 2017;45:310-319. doi: 10.1159/000458768
5. Arenas MD, Villar J, Gonzalez C, Cao H, Collado S, Crespo M, et al. Manejo de la epidemia por coronavirus SARS-CoV-2 (Covid 19) en unidades de hemodiálisis. Nefrologia. 2020. doi:10.1016/j.nefro.2020.04.001
6. Basile C, Combe C, Pazzarelli F, Covic A, Davenport A, Kanbay M, et al. Recommendations for the prevention, mitigation and containment of the emerging SARS-CoV-2 (COVID-19) pandemic in haemodialysis centres. Nephrol Dial Transplant. 2020;35:737-741. doi: 10.1093/ndt/gfaa069.
7. Li J, Xu G. Lessons from the experience in Wuhan to reduce risk of COVID-19 infection in patients undergoing long-term hemodialysis. Clin J Am Soc Nephrol. 2020;15:717-9. doi: 10.2215/CJN.03420320.
8. Hayden FG, Alloreta JK, Kaiser DL, Gwaltney J Jr. Prevention of natural colds by contact prophylaxis with intranasal alpha 2-interferon. N Engl J Med. 1986;314:71-3.
9. Turner RB, Felton A, Kosak K, Kelsey DK, Meschievitz CK. Prevention of experimental coronavirus colds with intranasal a-2b interferon. J Inf Dis 1986;154:443-7.
10. Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;357:1777-89.
11. Meng Z, Wang T, Chen L, Chen X, Li L, Qin X, et al. An experimental trial of recombinant human interferon alpha nasal drops to prevent coronavirus disease 2019 in medical staff in an epidemic area. medRxiv 2020.04.11.20061473; doi: 10.1101/2020.04.11.20061473
12. Ministry of Public Health. Cuban Protocol against COVID 19. Available in: https://instituciones.sld.cu/facultadfinlay/carrilabarran/protoco-cuba-vs-covid-4-4-2020. Accessed: 20 may 2020.
13. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and Distribution of Chest Radiographic Findings in COVID-19 Positive Patients. Radiology. 2020;296(2):E72-8. doi: 10.1148/radiol.2020201160.

14. Peng QY, Wang XT, Zhang LN, Chinese Critical Care Ultrasound Study Group (CCLSG). Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic. Intensive Care Med. 2020;46(5):849-850. doi: 10.1007/s00134-020-05996-6.

15. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

16. Wang R, Liao C, He H, Hu C, Wei Z, Hong Z, et al. COVID-19 in hemodialysis patients: a report of 5 cases. Am J Kidney Dis. 2020 Mar 31: S0272-6386(20)30612-0. doi: 10.1053/j.ajkd.2020.03.009.

17. Yuan H, Guo E, Gao Z, Hu F, Lu L. Coronavirus Disease 2019 in a Hemodialysis Patient. Blood Purif 2020. doi: 10.1159/000507877.

18. Douglas RM, Albrecht JK, Miles HB, Moore BW, Read R, Worwick DA, Woodward AJ. Intranasal interferon-alpha 2 prophylaxis of natural respiratory virus infection. J Infect Dis. 1985;151:731-6.

19. Turner RB, Felton A, Kosak K, Kelsey DK, Meschievitz CK. Prevention of Experimental Coronavirus Colds with Intranasal α-2b Interferon. J Infect Dis. 1986;154(3): 443-7.