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Interferon beta-1a as a Candidate for COVID-19 Treatment; An Open-Label Single-Arm Clinical Trial

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Abstract

Introduction: Since December 2019, an outbreak of Covid-19 has caused growing concern in multiple countries. Researchers around the world are working to find a treatment or a vaccine for Covid-19 and different treatment approaches have been tested in this regard.

Objective: This study was designed and conducted to assess the possible efficacy of Interferon beta-1a as a safe and efficient candidate for Covid-19 treatment.

Methods: This is an investigator-initiated, open-label, single-arm clinical trial. Twenty patients with suspected Covid-19, who were admitted to Sina hospital in Tehran, Iran, with moderate to severe symptoms, from 6 to 10 March, 2020, were enrolled. Patients were treated with antiviral and hydroxychloroquine combination therapy, along with subcutaneous Interferon beta-1a for 5 consecutive days. Baseline characteristics and findings during the course of admission and 5 days after discharge were recorded for all the patients.

Results: In total, 20 patients with suspected Covid-19 were included in this study, 12 (60%) of which were male. The median (Interquartile (IQ) range) of patients' age was 55.5 (43-63.5). The most common symptom of the patients at onset of disease was fever. The median (IQ range) of duration of hospital stay was 5.0 (3-6) days. Only 2 cases were admitted to ICU. At the time of follow-up, 15 (94%) patients reported that they generally felt good and had oral tolerance, 1 patient had suffered from dyspnea, 5 patients had suffered from cough, none of them had experienced fever and no case of re-admission or death was reported after discharge.

Conclusions: Results of the current study are in favor of using Interferon beta-1a in addition to recommended antiviral treatment in Covid-19 patients.

Key words: Antiviral Agents; Clinical Trials as Topic; COVID-19; Interferon beta-1a

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INTRODUCTION

In December 2019, some cases of pneumonia were reported in Wuhan, China, which were different from known pneumonia. The virus causing this disease was later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1, 2). The disease caused by this virus is rapidly spreading around the world and according to the World Health Organization (WHO) report, more than 4 million cases had been confirmed by 15 May 2020 (3) and therefore, it has been announced as a public health emergency and a pandemic (3).

The first case of Covid-19 in Iran has been detected on 19th of February, 2020 and after that we faced huge outbreak of this virus around the country. Until 15 May, 2020, Iran has had about 117,000 confirmed cases of Covid-19 and has ranked second in Asia after China. Researchers around the world are working to find a treatment or a vaccine for Covid-19 and different treatment approaches have been tested in this regard (4-6). SARS-CoV-2 is genetically related to the previously known coronavirus, SARS-CoV, with more than 79%

similarity between their sequences, which may lead to the effectiveness of SARS-CoV medicines in treatment of SARS-CoV-2 (4, 7).

Interferons have been evaluated in several studies in this regard and results indicate its efficacy in SARS-CoV-infected patients (8-11). In the study by Cinatl et al., it was shown that Interferons inhibit SARS-CoV replication in vitro and improve efficacy of antiviral drugs; moreover, this analysis indicated more potency for Interferon-beta compared to Interferon-alpha or gamma (8). This introduces this medicine as a candidate in combination with other antiviral drugs in the treatment of SARS or Covid-19 (8). Cell culture and animal studies also confirmed that Interferon (alpha/beta) should be administered as high-dose to be effective against SARS-CoV and MERS-CoV and this should be considered for patients (12). Furthermore, studies recommended that Interferon therapy should be initiated as early as possible when the disease is diagnosed, which can be due to its antiviral function and prophylaxis in non-infected cells (11, 13). As a result, Interferons, which are approved medications against several viral and autoimmune diseases, may offer the possibility of both prevention and treatment of Covid-19 in combination with antiviral drugs (14, 15). This study was designed and conducted to assess the possible efficacy of Interferon beta-1a as a safe and efficient candidate for Covid-19 treatment.

Methods

Study design and patient enrollment

This is an investigator-initiated, open-label, single-arm trial focusing on the clinical data of confirmed cases of Covid-19 in Sina Hospital in Tehran city, Iran, during 6-10 March, 2020. Using non-random sampling methods, 20 eligible patients were enrolled after signing the consent form.

Since the outbreak of Covid-19, specific hospitals were designated as main centers for Covid-19 patients. All suspected patients were transferred to these hospitals for confirmation and isolation. Considering the hospital-approved protocol, and due to delay in receiving the results of real time polymerase chain reaction (PCR) tests for confirmation of the disease and the patients were admitted based on clinical judgment and chest computed tomography (CT) scan findings. We sent a sample for PCR, but did not delay the treatment for receiving the positive result. To cope with the shortage of hospital beds, Sina Hospital did not admit patients who had O_2 saturation >93%, and stable vital signs and no underlying disease (diabetes mellitus, hypertension, ischemic heart disease, malignancy, asthma, use of corticosteroids and etc.), and had "mild" findings on their chest CT scan. A radiology resident and an attending emergency physician evaluated the chest CT scan of all suspected patients (16). To determine involvement severity on chest CT scan, each of the five lung lobes were assessed and amount of involved area in each lobe was scored as 0 for none, 1 for 1-25%, 2 for 26-50%, 3 for 51-75% and 4 for 76-100%. An overall lung severity score was calculated by summing the five lobe scores (ranged between 0-20) (17). We defined mild involvement as a score of 5 or less, moderate involvement as a score of 6-14 and severe involvement as a score of 15-20. Pregnant patients, those who were breast-feeding and those who had known allergy to Interferon beta, were excluded. The trial was approved by ethical committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.026) and registered in Iranian Registry of Clinical Trials (IRCT20150914024017N1).

Treatment regimen

Routine treatment protocol for Covid-19 patients in Sina Hospital was a combination of medications based on available evidence at the time and clinical judgment of the treating physician. The treatment protocols included hydroxychloroquine (200 mg twice daily), Lopinavir/Ritonavir (200/50mg four times daily), Oseltamivir (75 mg, twice daily) and Ribavirin (1200 mg twice daily) during hospitalization. We added ReciGen (Interferon beta 1-a, CinnaGen Co., nationally approved biosimilar of Rebif®) subcutaneous administration (44µg every day until discharge or until 5th day of admission, either one that came first) to the routine treatment protocols of the patients.

Clinical laboratory measurements

Routine lab tests including white blood cell (WBC) count, lymphocyte count, sodium, potassium, creatinine, lactate dehydrogenase and C-reactive protein (CRP) for each patient were performed on the day of admission. Oxygen was administered for hypoxic patients using either nasal cannula or facial mask, and cardiac monitoring was performed for all patients. The patients' vital signs and O_2 saturation were recorded at the time of admission and during the hospital stay until discharge. The need for intensive care unit (ICU) admission and intubation was evaluated by the treating physician daily or whenever the patient's situation exacerbated. Patients suspected of SARS-CoV-2 were discharged based on the hospital protocol, once they became afebrile with normal O_2 saturation in room air, and without dyspnea. All of

the patients were followed for 5 days after being discharged from the hospital via telephone calls and all conditions or adverse events were recorded.

Statistical analysis

In this study, continuous variables were depicted as either mean ± standard deviation (SD) or median with interquartile (IQ) range. Some of the variables were categorized and data were also presented for each category. All analyses were done using free R-3.6.1 version of RStudio software.

RESULTS

In total, 20 patients with suspected Covid-19, were included in this study, 12 (60%) of which were male. The median (IQ) of patients' age was 55.5 (43-63.5) years. The youngest patient was 26 years old and the oldest was 73 years old. The baseline characteristics of the studied patients are shown in table 1. Based on the findings, 15 patients had at least one known underlying disease and 5 patients (25%) did not have any. It is obvious that all of the patients had abnormal chest CT scan on the day of admission.

Vital signs of the studied patients during the 5-day treatment period are reported in table 2. The most common symptom of the patients at onset of disease was fever. Also, 10 (50%) patients had O_2 saturation less than 93% on the day of admission.

Serial laboratory findings of the patients are reported in table 3; On the first day of hospitalization, white blood cell count was less than 4×10^3/µl (leucopenia) in 3 (15%) patients, between 4-10×10^3/µL in16 patients, and more than 10×10^3/µl in one patient. Furthermore, lymphocyte count of 8 (40%) patients, hemoglobin level of 2 patients (10%), and platelet count of 6 (30%) patients was outside the normal range on the day of admission.

The frequency of applying each treatment regimen, findings during hospital stay, and length of hospital stay of the studied patients are reported in table 4. Of the 20 patients, 2 were admitted to ICU, one of them was later discharged and one of them died after 45 days of hospitalization. The mean (±SD) of hospital stay was 6.75 (±9.2) days. All of the patients received at least one antiviral treatment in their treatment combination regimen. Positive PCR results for Covid-19 were reported in only 6 (30%) patients.

We screened the patients for adverse events during hospitalization and no case of adverse events were reported. Fever, dyspnea, and oral tolerance were recorded, separately, as clinical features of Covid-19. Five days after discharge of the patients from the hospital, the patients were followed up by telephone call to record their data and 16 patients were reached after calling twice. One of the patients had died after being discharged and was

Table 1: Baseline characteristics of studied patients (n=20)

Characteristics	n (%)
Age (years)	
≤ 40	3 (15.0)
41 – 60	9 (45.0)
≥ 61	8 (40.0)
Sex	
Male	12 (60.0)
Female	8 (40.0)
Medical history	
Hypertension	5 (25.0)
Diabetes mellitus	6 (30.0)
Chronic obstructive pulmonary disease	1 (5.0)
Cardiovascular disease	2 (10.0)
Immunosuppressant use in past 2 weeks	2 (10.0)
Corticosteroid use in past 2 weeks	2 (10.0)
Chronic kidney disease	1 (5.0)
None	5 (25.0)
Number of consolidated lobes in chest CT scan	
3	1 (5.0)
6-7	3 (15.0)
8-9	4 (20.0)
10-11	3 (15.0)
12-13	2 (10.0)
Imaging not available	7 (35.0)

Table 2: Vital signs of the studied patients during the 5-day treatment period

Variable	Day 1 (n=20)	Day 2 (n=20)	Day 3 (n=18)	Day 4 (n=13)	Day 5 (n=11)
Temperature; mean±SD (°C)	37.5±0.69	37.3±0.82	37.3±0.67	37.8±0.98	37.2±0.65
< 37.3	8 (40.0)	11 (55.0)	11 (61.1)	5 (38.5)	7 (63.7)
37.3 – 38.0	8 (40.0)	7 (35.0)	5 (27.8)	3 (23.7)	3 (27.3)
38.01 – 39.0	4 (20.0)	1 (5.0)	1 (5.6)	3 (23.7)	1 (9.1)
> 39.0	0 (0.0)	1 (5.0)	1 (5.6)	2 (15.4)	0 (0.0)
Respiratory rate; mean±SD (/min)	25.1±7.9	21.2±5.7	21.6±7.3	23.7±5.8	25.6±5.9
Respiratory rate >24 breaths per min	7 (35.0)	5 (25.0)	5 (27.8)	4 (30.8)	4 (36.4)
Pulse rate; mean±SD (/min)	86.9±13.7	81.4±9.8	76.9±9.2	79.4±9.1	74.8±6.7
Systolic Blood Pressure; mean±SD (mmHg)	120.9±14.2	121.7±17.4	120.6±13.5	118.7±10.6	118.4±10.0
Diastolic Blood Pressure; mean±SD (mmHg)	73.1±10.1	77.9±12.8	71.6±10.5	73.8±9.6	72.3±11.3
O_2 Saturation; mean±SD (%)	93.0±5.4	93.9±5.3	95.3±3.6	92.4±4.6	90.3±4.7

Values are presented as mean±SD, or frequency (percent).

Table 3: Serial laboratory findings of the studied patients

Characteristics	Day 1 (n=20)	Day 2 (n=13)	Day 3 (n=7)
White blood cell count (×10³/µl)	5.9 (4.6 – 7.2)	4.3 (4.1 – 6.1)	4.2 (3.7 – 5.9)
< 4	3 (15.0)	2 (15.4)	3 (42.9)
4 – 10.5	16 (80.0)	11 (84.6)	4 (57.1)
> 10.5	1 (5.0)	0 (0.0)	0 (0.0)
Lymphocyte count (%)	20.7 (17.3 - 32.0)	25.3 (18.6 – 30.7)	25.3 (22.5 – 34.2)
<20	8 (40.0)	4 (30.8)	1 (14.3)
20-45	12 (60.0)	8 (61.5)	6 (85.7)
>45	0 (0.0)	1 (7.7)	0 (0.0)
Hemoglobin (mg/dl)	14.3 (13.0 – 14.8)	13.1 (11.5 – 13.9)	12.4 (8.5 – 12.8)
Platelet count (×10³/µl)	204.5 (129 – 264.3)	212.0 (161 – 266)	221.0 (159 – 317)
< 150	6 (30.0)	2 (15.4)	1 (14.3)
≥ 150	14 (70.0)	11 (84.6)	6 (85.7)
Sodium (meq/L)	136 (131.0 - 137.9)	-	-
Potassium (meq/L)	4.1 (3.9 – 4.5)	-	-
Creatinine (mg/dl)	1.0 (0.9 – 1.3)	-	-
< 0.7	0 (0.0)	-	-
0.7 – 1.4	16 (80.0)	-	-
> 1.4	4 (20.0)	-	-
Lactate dehydrogenase	577 (469.0 – 963.5)	-	-
C-reactive protein	60.2 (32.5 – 122.6)	-	-

Analysis was based on the available data, missing data were not considered. Values were presented as median (interquartile, IQ), or frequency (percent)

Table 4: Frequency of applying each treatment regimen, findings during hospital stay, and length of hospital stay of the studied patients

Category	Value
Treatment	
Hydroxychloroquine-Oseltamivir-Lopinavir/Ritonavir-ReciGen (Interferon beta-1a)	10 (50.0)
Hydroxychloroquine-Oseltamivir-Lopinavir/Ritonavir-Ribavirin-ReciGen (Interferon beta-1a)	8 (40.0)
Oseltamivir-Lopinavir/Ritonavir-Ribavirin	1 (5.0)
Oseltamivir – Lopinavir/Ritonavir	1 (5.0)
Patients who received Vancomycin	7 (35.0)
In-hospital findings	
Number of patients who required admission in ICU	2 (10.0)
Number of patients who required intubation	1 (5.0)
Admission to emergency room, Median (IQ), days	0 (0-0)
Hospitalization, days	5.0 (3-6)
Duration of oral tolerance during hospital administration, Median (IQ), days	3 (2-4)
Duration of dyspnea situation, Median (IQ), days	1.5 (0.3-3)
Number of patients who suffered from dyspnea	15 (75.0)
Death	0 (0.0)

Values were presented as median (interquartile, IQ), or numbers (percentages)

not considered for follow-up. In this step, 15 patients reported that they generally felt good, all of them had oral tolerance, 1 of the patients had suffered from dyspnea, 5 of the patients had suffered from cough, none of them had experienced fever and no case of re-admission or death was reported after discharge.

Discussion

All of the patients in the current study were treated with Interferon beta-1a plus different combination treatments including antiviral drugs. Interferon beta-1a has been used in high dose on the first day of hospital admission. This dosage of Interferon beta-1a, 44µg, has been approved for treatment of multiple sclerosis two decades ago and using high dose of Interferon beta-1a, as a natural antiviral protein, has been reported to be safe in other indications like hepatitis (18). After the first administration of the drugs, patients' clinical features improved and only one case of death was reported after 45 days of hospitalization. Moreover, other outcomes of patients were satisfactory and the mean duration of hospital stay for all of the patients was 6.75 days.

Since Covid-19 was announcement to be a pandemic, finding the appropriate or effective treatment for this disease is crucial and various available antiviral agents in combination with other drugs are being evaluated. Based on previous data about the efficacy of Interferon beta against SARS-CoV (8, 9, 12, 14) and the similarity of this

virus with SARS-CoV-2 (19), Interferon beta-1a was added to the antiviral combination treatment of patients. SARS-CoV-2 enters the cell through interaction with host receptor Angiotensin-Converting Enzyme 2 (ACE2), and then its positive stranded genome is released and its replication is initiated (19). The next steps of replication, transcription and translation lead to initiation of innate immune responses (11, 20). While the synthesis of Interferon, as a defensive mechanism of human, normally increases after a viral infection and this phenomenon can limit the viral infection, several studies have reported that Interferon production was limited after infection with SARS-CoV (11, 20). Furthermore, several in-vitro studies reported that Interferon effectively restrains the replication of SARS-CoV, and this data indicate the efficacy of exogenous Interferon for treatment of SARS-CoV (8, 9, 11). Therefore, it seems that Interferon beta is one of the medications that can be used in combination with other antiviral drugs for management of Covid-19.

Limitations

Due to the Covid-19 pandemic and geopolitical situation of Iran, this study has several limitations. Firstly, only 20 patients were studied. A large number of patients were continually being admitted to Sina hospital, and due to the false negative results of PCR, we decided to consider other criteria for diagnosis of new corona virus infection. Secondly, based on the evidence available at the time and several updates in guidelines, patients did not receive the same standard treatment. Also, there was not a control group to compare the results with. To further investigate the effects of Interferon beta-1a in Covid-19, a two-armed parallel trial has been designed and started by the same team (IRCT20150914024017N1).

Conclusions

Results of the current study are in favor of using Interferon beta-1a in addition to recommended antiviral treatment in Covid-19 patients. However, for confirming its efficacy and safety, two-armed randomized parallel clinical trials are needed.

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Authors' contribution

PP and MS conceptualized the paper. MA and SS analyzed the data, with input from AH, FN, SS, MP and HB. RR was involved with pharmacological advice and design of the study. PP wrote the initial draft with all authors providing critical feedback and edits to subsequent revisions. All authors approved the final draft of the manuscript. MS was the guarantor. All authors agree to be accountable for all aspects of the work and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

Dr. Morteza Azhdarzadeh is an employee of the CinnaGen co. and has no other conflict of interest. All other authors have no conflict of interest to declare.

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