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RESEARCH ARTICLE

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Study of the effects of interferon β−1a on hospitalized patients with COVID-19: SBMU Taskforce on the COVIFERON study

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Abstract

Interferons are an essential part of the innate immune system and have antiviral and immunomodulatory functions. We studied the effects of interferon β-1a on the outcomes of severe cases of coronavirus disease 2019 (COVID-19). This retrospective study was conducted on hospitalized COVID-19 patients in Loghman-Hakim hospital from February 20, 2020 to April 20, 2020, Tehran, Iran. Patients were selected from two groups, the first group received interferon β-1a in addition to the standard treatment regimen, and the second group received standard care. The clinical progression of two groups during their hospital admission was compared. We studied a total number of 395 hospitalized COVID-19 patients. Out of this number, 111 patients (33.5%) died (31.3% of the interferon β-1a group and 34.1% of the control group). The mortality rate indicated no statistically significant difference between groups (p-value = 0.348), however for patients who were hospitalized for more than a week, the rate of mortality was lower in the interferon β-1a group (p-value = 0.014). The median hospital stay was statistically longer for patients treated by interferon β-1a (p-value < 0.001). The results of this study showed that interferon β-1a can improve the outcomes of hospitalized patients with severe COVID-19, but more adequately-powered randomized controlled trials should be conducted.

KEYWORDS
COVID-19, efficacy, IFN-β1a, outcome

1 | INTRODUCTION

In December 2019, a new virus belonging to the coronaviridea family was reported in Wuhan, China, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus caused a global outbreak of a respiratory disease known as coronavirus disease 2019 (COVID-19).[1] COVID-19 has a wide range of symptoms including mild self-limited disease to severe progressing pneumonia and multiple organ failure.[2–4] The high rate of transmission and mortality (3.7%) of this disease[5] made it a public health emergency of international concern (PHEIC).[6]

Clinical researchers made efforts to find a specific treatment for COVID-19, and have suggested some kind of medications for the management of this disease.[7,8] The efficacy of different categories of drugs have been evaluated in clinical trials and some medications had relative efficacy.[9] The emergency condition of the COVID-19 pandemic and lack of available drugs of proven efficacy for COVID-19 caused to repurpose drugs for treating COVID-19 which were used for other purposes previously.[10] Various pharmacological interventions were suggested to treat COVID-19, however, their efficiency is questionable. Some antiviral agents, including remdesivir and combination of lopinavir and ritonavir, and immunomodulatory drugs, consisting of corticosteroids, hydroxychloroquine, and interferons, have been used in COVID-19 patents.[11–16]

The innate immune response plays an important role in novel viral infections without previous established adaptive immunity to the pathogen to downturn the severity of the disease.[17] Interferons are an essential part of this immune action and have antiviral and immunomodulatory functions.[17] In a recent clinical trial, interferon beta1-a (IFN-β1a) had significant efficacy in patients with COVID-19.[16] Previous in vitro investigations showed the antiviral effect of interferon-β against the SARS virus.[18] In this retrospective study, we assessed the clinical results of IFN-β1a in severe cases of COVID-19.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This retrospective study was conducted on hospitalized COVID-19 patients in Loghman-Hakim hospital from February 20, 2020 to April 20, 2020, Tehran, Iran. This study started after research ethics committee approval. Patients were selected from two groups with different treatment regimens for COVID-19, which were matched, based on age, sex, and severity of disease regarding arterial oxygen saturation. Patients of the first group received interferon β-1a (IFN-β1a) (Recigen) in addition to standard treatment regimen and patients of the second group received standard care. We obtained demographic characteristics, background health conditions, clinical symptoms, and signs, and laboratory and imaging findings of patients.

2.2 | Patients

We studied patients with COVID-19 which was confirmed by positive polymerase chain reactions (PCRs) and positive chest computed tomography (CT) scans. All patients had clinical symptoms accordant with COVID-19. Participants were hospitalized in the ward or intense care unit of Loghman Hospital due to severe COVID-19 pneumonia. Severe COVID-19 was defined as patients with arterial blood oxygen saturation level less than 90 percent in the initial assessment and who suffer from moderate to severe dyspnea, based on patients' assessment. Some of these patients had received IFN-β1a in addition to standard treatment regimen and the rest had received just standard care. Patients of these two groups were matched, based on age, sex, and the severity of the disease. Clinical information of patients has been extracted from Loghman-Hakim hospital central database.

2.3 | Treatment

In this study, the patients were selected from two groups. Both groups received medication based on the protocol of the health ministry of Iran for COVID-19 including lopinavir/ritonavir (400 mg/100 mg twice a day for 10 days) (Kaletra) + hydroxychloroquine (400 mg single dose). This treatment regimen was based on Iran's internal guideline for COVID-19 in February 2020, when we initiated this study.[19] Patients of the first group also received IFN-β1a (subcutaneous injections of 44 μg (12 000 000 IU) on Days 1, 3, and 5), (Recigen).

2.4 | Outcomes

We studied the clinical progression of two groups during their hospital admission. The mortality rate in the early 7 days and in the late phase of admission, duration of hospital admission, arterial blood gas findings, complete blood count findings, C-reactive protein, and erythrocyte sedimentation rate have been compared between two groups.

2.5 | Statistical analysis

Frequency rates and percentages were used for categorical variables, and interquartile ranges (IQRs) and median were used for continuous variables. For comparison of the non-normal continuous variables, the Kruskal–Wallis test was used. χ^2 test was used for comparing the frequency of categorical variables and a logistic regression model was also applied to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). R software version 3.6.1 was used to perform the statistical analyses.

TABLE 1 Characteristics of the patients at baseline

Parameters	Total (*n* = 331)	Interferon (*n* = 64)	Standard Care (*n* = 267)	*p*-value
Characteristics				
Age (year)	64.9 (18.2)	62.9 (22.1)	65.4 (17.1)	0.413
Male sex - no. (%)	203 (61.3%)	34 (53.1%)	169 (63.3%)	0.153
Underlying conditions				
Diabetes	107 (32.33%)	17 (26.56%)	90 (33.71%)	0.301
Hypertension	142 (42.90%)	30 (46.88%)	112 (41.95%)	0.485
Cardiovascular disease (CVD)	78 (23.56%)	17 (26.56%)	61 (22.85%)	0.516
Rheumatologic condition	6 (1.81%)	3 (4.69%)	3 (1.12%)	0.089
Asthma	15 (4.53%)	2 (3.13%)	13 (4.87%)	0.744
COPD	23 (6.95%)	5 (7.81%)	18 (6.74%)	0.785
Chronic liver disease	1 (0.3%)	1 (1.56%)	0 (0%)	1.000
Transplant receiver	5 (1.51%)	3 (4.69%)	2 (0.75%)	0.526
Malignancy	7 (2.11%)	1 (1.56%)	6 (2.25%)	0.594
HIV	8 (2.42%)	4 (6.25%)	4 (1.50%)	0.048
Hepatitis B	1 (0.3%)	1 (1.56%)	0 (0%)	1.000
Hypothyroidism	5 (1.51%)	0 (0%)	5 (1.87%)	0.587
Respiratory factors				
Oxygen saturation (SpO_2) — median (IQR)	50.1 (35.48–75.2)	57.8 (35.7–83.9)	47.6 (35.3–73.43)	0.157
pH (DISS) - median (IQR)	7.4 (7.37–7.46)	7.4 (7.36–7.47)	7.4 (7.37–7.46)	0.512
$PaCO_2$ (DISS) - median (IQR)	38.1 (32.08–46.1)	38.2 (30.7–48.13)	39.2 (32.2–46.07)	0.382
PaO_2 (DISS) - median (IQR)	26.9 (21–40.8)	29.5 (20.8–44.2)	26.3 (21–39.23)	0.879
HCO_3 (DISS) - median (IQR)	27.7 (23.5–27.5)	26.3 (24–27.5)	25.5 (23.1–27.5)	0.041
Respiratory rate	19 (17–22)	18 (16–20)	19 (18–22)	<0.001
White blood cell count ($\times 10^{-9}$/L) – median (IQR)	7.71 (5.6–10.6)	7.61 (5.6–10.75)	7.80 (5.6–10.6)	0.934
$<4 \times 10^{-9}$/L – no. (%)	23 (7.26%)	4 (6.25%)	19 (7.51%)	
$4–10 \times 10^{-9}$/L – no. (%)	200 (63.09%)	42 (65.62%)	158 (62.45%)	0.88
$>10 \times 10^{-9}$L– no. (%)	94 (28.84%)	18 (28.13%)	76 (30.04%)	
Lymphocyte count ($\times 10^{-9}$/L) – median (IQR)	0.96 (0.69–1.38)	0.89 (0.7–1.28)	0.96 (0.69–1.39)	0.653
$\geq 1.0 \times 10^{-9}$/L – no. (%)	139 (44.4%)	24 (38.1%)	115 (46%)	0.321
$<1.0 \times 10^{-9}$/L – no. (%)	174 (55.6%)	39 (61.9%)	135 (54%)	
Platelet count ($\times 10^{-9}$/L) – median (IQR)	192.5 (148–240.5)	203.5 (171–255.5)	189 (144–240.5)	0.174
$\geq 100 \times 10^{-9}$/L – no. (%)	301 (95.25%)	63 (98.34%)	236 (94.4%)	0.180
$<100 \times 10^{-9}$/L – no. (%)	15 (4.75%)	1 (1.56%)	14 (5.6%)	
Neutrophil count ($\times 10^{-9}$/liter) – median (IQR)	6.15 (4.11–8.97)	5.92 (3.71–9.17)	6.16 (4.19–8.93)	0.654
$<1.5 \times 10^{-9}$/L – no. (%)	7 (2.36%)	2 (3.23%)	5 (2.13%)	
$1.5–8 \times 10^{-9}$/L – no. (%)	193 (64.98%)	41 (66.13%)	152 (64.68%)	0.834
$>8 \times 10^{-9}$/L – no. (%)	97 (32.66%)	19 (30.64%)	78 (33.19%)	
Aspartate aminotransferase (AST) (U/L) – median (IQR)	56 (38–85)	59 (46.5–78.2)	55 (37–86)	0.915
≤40 U/L – no. (%)	67 (27.34%)	10 (17.24%)	57 (%)	0.032
>40 U/L – no. (%)	178 (72.66%)	48 (82.76%)	130 (%)	

(Continues)

TABLE 1 (Continued)

Parameters	Total (*n* = 331)	Interferon (*n* = 64)	Standard Care (*n* = 267)	*p*-value
Alanine aminotransferase (ALT) (U/L) – median (IQR)	59 (38–98)	53.4 (37–96)	59.5 (38–99.25)	0.802
≤50 U/L – no. (%)	104 (42.79%)	26 (45.62%)	78 (41.94%)	0.366
>50 U/L – no. (%)	139 (57.21%)	31 (54.38%)	108 (58.06%)	
Lactate Dehydrogenase (LDH) (U/L) - median (IQR)	444.5(301–687.5)	578(383-845)	428(283.5–643)	0.398
≤245 U/L – no. (%)	18 (15.25%)	3 (9.09%)	15 (17.65%)	0.193
>245 U/L – no. (%)	100 (84.75%)	30 (90.91%)	70 (82.35%)	
C-reactive protein (CRP) - median (IQR)	57.05 (29.5–82.9)	48.5 (25.65-69.5)	60 (33.55–83.65)	0.121
CRP < 6 – no. (%)	20 (9.71%)	7 (14.28%)	13 (8.28%)	0.267
CRP > 6 – no. (%)	186 (90.29%)	42 (85.72%)	144 (91.72%)	
Erythrocyte sedimentation rate (ESR) - median (IQR)	48 (25–69)	48 (22–71)	48 (25–68)	0.556
Serum creatinine (μmol/L) - median (IQR)	1.3 (1–1.6)	1.1 (1-1.475)	1.3 (1.1–1.7)	0.412

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

TABLE 2 Outcomes

Parameters	Total (*n* = 331)	Interferon (*n* = 64)	Standard care (*n* = 267)	*p*-value
Mortality	111 (33.5%)	20 (31.3%)	91 (34.1%)	0.768
Early Mortality* - no. (%)	72 (21.75%)	14 (21.87%)	58 (21.72%)	0.348
Late Mortality** - no. (%)	39 (15.06%)	6 (12.00%)	33 (15.78%)	0.014
Hospital stay — median no. of days (IQR)	4 (2–7)	7 (5–9)	4 (2–7)	<0.001

*Mortality before 7 days of hospitalization.

**Mortality after 7 days of hospitalization.

3 | RESULTS

In this retrospective study, which was conducted on hospitalized patients in Loghman-Hakim hospital from February 20, 2020 to April 20, 2020, Tehran Iran with severe COVID-19 pneumonia, was confirmed by positive reverse-transcription polymerase chain reaction and positive chest CT scans. We studied a total number of 395 patients in this study, and from them, 64 patients received IFN-β1a (Recigen) plus the standard care (lopinavir/ritonavir [Kaletra] + hydroxychloroquine) and 331 control patients received standard care.

The mean (±*SD*) age of total patients was 64.9 (18.2) with the majority being male (61.3%). There were no statistically significant differences in age and sex between the two groups. In Table 1, the demographic and clinical factors across two study groups were presented (Table 1). Although most clinical factors were distributed similarly across the two groups, the rate of HIV infection, HCO_3, and respiratory rate were statistically different between the two groups (Table 1). Out of the 395 patients under study, 111 patients (33.5%) died (31.3% of the Recigen group and 34.1% of the control group). The mortality rate indicated no difference between the groups, however for patients who were hospitalized for more than a week, the rate of mortality was lower in the Recigen group, compared to the corresponding group among those who received only the standard care (12.00% mortality in Recigen group vs. 15.78% mortality in the control group, Table 2). Also, the median hospital stay was statistically longer for patients treated by IFN-β1a (median 7 days in the Recigen group vs. 4 days in the control group, *p*-value < 0.001) (Table 2).

From other clinical factors, the median of white blood cell count, lymphocyte count, and neutrophil count was not significantly different between the Recigen group and the controls. Also, we used a logistic regression model to calculate the odds ratio of mortality for patients who were just treated by the standard care, compare to the Recigen group. According to analysis in a crude model, the odds of death in control groups, compared to the Recigen group was 1.13 (95% CI: 0.63–2.04, *p* value = 0.67) and the adjusted odds ratio (for respiratory rate, saturation, and HCO_3) was 1.13 (95% CI: 0.58–2.18, *p* value = 0.71). As the mortality was lower for the Recigen group in patients with more than one week of hospitalization, we did a subgroup analysis for those patients. The results indicated a substantial significant difference between the two groups; the crude odds ratio was 3.96 (95% CI: 1.37–11.43, *p* value = 0.011) as similar as the

adjusted odds ratio, which was 4.02 (95% CI: 1.22–13.21, p value = 0.022), which revealed that patients who were treated with standard care and hospitalized for at least one week were at higher risk of death, compared to same patients who treated with Recigen.

4 | DISCUSSION

This study revealed that IFN-β1a decreased the days of hospitalization and the mortality rate in severe COVID-19 patients who had been hospitalized for more than 7 days.

The mortality rate in severe COVID-19 patients was reported between 62% and 81%.[20] A recent study showed COVID-19 patients with more severe disease had significantly decreased interferon activity and SARS-CoV-2 suppressed IFN-β release in vitro.[21,22] There is an increased risk of severe lung disease in people with comorbidities, older age, or who receive immunosuppressive medication due to less IFN-β production.[23,24]

IFN-β is superior to other interferons in inhibition of coronaviruses replication.[25] It should be used in the early phase of viral infection to reach a protective effect and late application of interferon may exacerbate the disease.[26,27] IFN-β increases CD73 which plays a role in vascular integrity in hypoxic conditions.[28] A high serum level of interferon is needed to reach an antiviral effect.[27] Long-term safety and tolerability of IFN-β are proven due to its application in multiple sclerosis treatment.[29]

In our study, the two groups didn't have a significant difference in mortality rate; however, in patients who were hospitalized for more than a week, the rate of mortality was lower in the Recigen group, compared to those corresponding ones who received standard care. In addition, the median hospital stay was statistically longer for patients treated by IFN-β1a.

In a previous randomized trial, a combination of INF-β with lopinavir/ritonavir and ribavirin was safe, alleviated the symptoms, and shortened the duration of hospital stay compared with triple antiviral therapy alone.[30]

In another trial, IFN-β significantly improved the discharge rate and lowered the 28–day mortality, especially in patients who received it in the early phase of the disease.[31]

We had some limitations in this study. The most important limitation is that this study was conducted in the critical phase of the COVID-19 outbreak in Iran when we didn't have enough information about COVID-19, so treatment was not conforming to COVID-19. In addition, there might be some problems in the data gathering, group matching, and homogeneity of the patients at the beginning of this outbreak. Considering the above limitations, we didn't design this study as a randomized clinical trial.

5 | CONCLUSION

Although the results of this study showed that IFN-β1a can improve the outcomes of severe COVID-19 patients, more adequately-powered randomized controlled trials should be conducted to determine the initiation time, dose, and duration of treatment of IFN-β1a in severe COVID-19 patients.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

This study was approved by the research ethics committees of the Shahid Beheshti University of Medical Science and the ethical code number is IR. SBMU. RETECH. REC.1399.079.

AUTHOR CONTRIBUTIONS

Mohammad Fallahzadeh, Ilad Alavi Darazam, and Sajad Besharati prepared the first draft. Mahdi Amir Pourhoseingholi conducted the analysis on data and edited the first draft. Masoud Ghanbari Boroujeni and Ilad Alavi Darazam finalized all drafts, approved the final version of the manuscript, and made the decision to submit the results. Seyed Sina Naghibi Irvani conceived of the study and provided overall guidance. Ilad Alavi Darazam, Shervin Shokouhi, Minoosh Shabani, Mahdi Amirdosara, Mohammadreza Hajiesmaeili, Masoud Mardani, Golshan Mirmomeni, and Masoud Zangi were involved in conducting the trial, recruited patients, and took clinical care of the patients. All other authors gathered data, reviewed and interpreted results, or provided guidance on methodology. All authors critically reviewed and revised the manuscript, and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data presented in the manuscript could be available for the journal.

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