Efficacy of Interferon β-1a in Treatment of Hospitalized COVID-19 Patients; SBMU Taskforce on the COVIFERON Study

Mohammad Fallahzadeh
Shahid Beheshti University of Medical Sciences School of Medicine
Mohamad Amin Pourhoseingholi
Shahid Beheshti University of Medical Sciences Research Institute for Gastroenterology and Liver Diseases
Sajad Besharati
Shahid Beheshti University of Medical Sciences School of Medicine
Masoud Ghanbari Boroujeni
Shahid Beheshti University of Medical Sciences School of Medicine
Masoud Mardani
Shahid Beheshti University of Medical Sciences School of Medicine
Minoosh Shabani
Shahid Beheshti University of Medical Sciences School of Medicine
Shervin Shokouhi
Shahid Beheshti University of Medical Sciences School of Medicine
Mahdi Amirdosara
Shahid Beheshti University of Medical Sciences School of Medicine
Mohammadreza Hajiesmaeili
Shahid Beheshti University of Medical Sciences School of Medicine
Latif Gachkar
Shahid Beheshti University of Medical Sciences School of Medicine
Baran Roshan
Shahid Beheshti University of Medical Sciences School of Pharmacy
Masoud Zangi
Shahid Beheshti University of Medical Sciences School of Medicine
Golshan Mirmomeni
Ahvaz Jondishapour University of Medical Sciences Faculty of Medicine
Seyed Sina Naghibi Irvani
Shahid Beheshti University of Medical Sciences School of Medicine
Ilad Alavi Darazam (ilad13@yahoo.com)
Shahid Beheshti University of Medical Sciences https://orcid.org/0000-0002-4440-335X

Research

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Abstract

Background: Interferons are essential part of the innate immune and have antiviral and immunomodulatory functions. In the lack of definite medication for COVID-19, Interferons can be effective in treatment of severe cases of COVID-19 and may decrease mortality of this disease.

Material and methods: This retrospective study was conducted on hospitalized COVID-19 patients in Loghman-Hakim hospital from 20 February 2020 to 20 April 2020, Tehran, Iran. Patients were selected from two groups, first group received Interferon β-1a in addition to standard treatment regimen and patients of second group received standard care. The clinical progression of two groups during their hospital admission have been compared.

Results: We studied total number of 395 hospitalized COVID-19 patients. Out of this number, 111 patients (33.5%) died (31.3% of Interferon β-1a (Recigen) group and 34.1% of control group). Mortality rate indicated no statistically significant difference between groups, however for patients who hospitalized more than a week, the rate of mortality was lower in Recigen group. The median time of staying in hospital was statistically shorter for patients treated by IFN-β1a. The Odds of death in control groups who hospitalized for at least one week, compared to Recigen group was 3.96 (95% CI: 1.37-11.43, P.value=0.011)

Conclusion: This study showed IFN-β1a have significant efficacy in treating severe COVID-19 patients who hospitalized for at least one week and improve the outcomes of patients and decrease the duration of hospitalization.

Introduction

In December 2019, a new virus belonging to corona viridea family reported in Wuhan, China which named SARS-CoV-2. This virus caused global outbreak of respiratory disease known as 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). High rate of transmission and mortality (3.7 %) of this disease(5) made it a public health emergency of international concern(PHEIC)(6).

Despite efforts for finding specific treatment for COVID-19, there is no definite treatment for this disease. Although, efficacy of different category of drugs have been evaluated in clinical trials and some medications had relative efficacy(7). Emergency condition of 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 (8). Various pharmacological interventions were suggested to treat COVID-19, however efficiency of them are questionable. Some of antiviral agents, including remdesivir and combination of lopinavir and ritonavir, and immunomudulatory drugs, consist of corticosteroids, hydroxychloroquine and interferons, have been used in COVID-19 patents (9–12).

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 disease (13). Interferons are essential part of this immune action and have antiviral and immunomodulatory functions (13). In recent clinical trials, interferon beta1-a had significant efficacy in severe cases of COVID-19. Previous in vitro investigations showed antiviral effect of interferon beta against SARS virus (14).

In this retrospective study, we assessed clinical result of interferon beta 1-a in severe cases of COVID-19.

Material And Method

Study design and setting:

This retrospective study was conducted on hospitalized COVID-19 patients in Loghman-Hakim hospital from 20 February 2020 to 20 April 2020, Tehran, Iran. This study started after research ethics committee approval and informed consent obtained from patients. 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 first group received IFN-β1a (Recigen) in addition to standard treatment regimen and patients of second group received standard care. We took demographic characteristics, background health condition, clinical symptoms and signs and laboratory and imaging findings of patients.

Patients:

We studied 395 patients with COVID-19 which confirmed by positive Polymerase chain reactions(PCRs) and positive chest CT scans. All patients had clinical symptoms accordant with COVID-19. Participants were hospitalized in ward or intense car unit of Loghman Hospital due to severe COVID-19 pneumonia. Patients selected for this study had arterial blood oxygen saturation level less than 90 percent in the initial assessment and were suffering from moderate to severe dyspnea. Some of these patients had received interferon beta-1a 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 severity of disease. Clinical information of patients have been extracted from Loghman-Hakim hospital central database.

Treatment:

In this study, 64 patients selected from first group and 331 patients selected from second group. Both groups received medication based on protocol of health ministry of Iran for COVID-19 including: lopinavir / ritonavir (400mg/100mg bid for 10–14 days) (Kaletra) + hydroxychloroquine (400mg single dose). This treatment regimen was based on Iran’s internal guideline for COVID-19 in February 2020, when we initiated this study(15). Patients of first group received interferon beta-1a (subcutaneous injections of 44μg (12,000 IU) on days 1, 3, 5), (Recigen).

Outcomes:

We studied the clinical progression of two groups during their hospital admission. 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.

Statistical analysis:

Frequency rates and percentages were used for categorical variables, and Interquartile Ranges (IQRs) and median were used for continuous variables. For comparison the non-normal continuous variables, Kruskal-Wallis test was used. Chi-Square test was used for comparing the frequency of categorical variables and Logistic regression model was also applied to calculate the ORs with 95% Confidence Intervals (CIs). R software version 3.6.1 was used to perform the statistical analyses.

Results

In this retrospective study which conducted on hospitalized patients in Loghman-Hakim hospital from 20 February 2020 to 20 April 2020, Tehran Iran which confirmed by positive RT-PCRs and positive chest CT scans, with severe COVID-19 pneumonia. From them, 64 patients received IFN-β1a (Recigen) and 331 control patients received standard care (lopinavir / ritonavir (Kaletra) + hydroxychloroquine).

The mean (± SD) age of total patients was 64.9 (18.2) with dominated of sex male (61.3%). There were no statistically significant differences of age and sex between 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 two groups, the rate of HIV infection, HCO3 and Respiratory rate were statistically different between two groups (Table 1). Out of the 395 patients under study, 111 patients (33.5%) died (31.3% of Recigen group and 34.1% of control group). Mortality rate indicated no statistically significant difference between groups, however for patients who hospitalized more than a week, the rate of mortality was lower in Recigen group, compared to those corresponding ones in who received standard care. Besides, the median time of staying in hospital was statistically shorter for patients treated by IFN-β1a (Table 2).

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 (SpO2) — 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
PaCO2 (DISS) - median (IQR)	38.1 (32.08–46.1)	38.2 (30.7-48.13)	39.2 (32.2-46.07)	0.382
PaO2 (DISS) - median (IQR)	26.9 (21-40.8)	29.5 (20.8–44.2)	26.3 (21-39.23)	0.879
HCO3(DISS) - median (IQR)	27.7 (23.5–27.5)	26.3 (24-27.5)	25.5 (23.1–27.5)	0.041

Parameters	Total (n = 331)	Interferon (n = 64)	Standard Care (n = 267)	p-value
Respiratory rate	19 (17–22)	18 (16–20)	19 (18–22)	< 0.001
White Blood Cell count (×10^{-9}/liter) — median (IQR)	7.71 (5.6–10.6)	7.61 (5.6-10.75)	7.80 (5.6–10.6)	0.934
< 4 ×10^{-9}/liter — no. (%)	23 (7.26 %)	4 (6.25 %)	19 (7.51 %)	
4–10 ×10^{-9}/liter — no. (%)	200 (63.09 %)	42 (65.62 %)	158 (62.45 %)	0.88
> 10 ×10^{-9}/liter— no. (%)	94 (28.84 %)	18 (28.13 %)	76 (30.04 %)	
Lymphocyte count (×10^{-9}/liter) — median (IQR)	0.96 (0.69–1.38)	0.89 (0.7–1.28)	0.96 (0.69–1.39)	0.653
≥ 1.0 ×10^{-9}/liter — no. (%)	139 (44.4 %)	24 (38.1 %)	115 (46 %)	0.321
< 1.0 ×10^{-9}/liter — no. (%)	174 (55.6 %)	39 (61.9 %)	135 (54 %)	
Platelet count (×10^{-9}/liter) — median (IQR)	192.5 (148-240.5)	203.5 (171-255.5)	189 (144-240.5)	0.174
≥ 100 ×10^{-9}/liter — no. (%)	301 (95.25 %)	63 (98.34 %)	236 (94.4 %)	0.180
< 100 ×10^{-9}/liter — no. (%)	15 (4.75 %)	1 (1.56 %)	14 (5.6 %)	
Neutrophil count (×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 ×10^{-9}/liter — no. (%)	7 (2.36 %)	2 (3.23 %)	5 (2.13 %)	
1.5-8 ×10^{-9}/liter — no. (%)	193 (64.98 %)	41 (66.13 %)	152 (64.68 %)	0.834
> 8 ×10^{-9}/liter — no. (%)	97 (32.66 %)	19 (30.64 %)	78 (33.19 %)	
Aspartate Aminotransferase (AST) (U/liter) — median (IQR)	56 (38–85)	59 (46.5–78.2)	55 (37–86)	0.915
≤ 40 U/liter — no. (%)	67 (27.34 %)	10 (17.24 %)	57 (%)	0.032
> 40 U/liter — no. (%)	178 (72.66 %)	48 (82.76 %)	130 (%)	
Alanine Aminotransferase (ALT) (U/liter) — median (IQR)	59 (38–98)	53.4 (37–96)	59.5 (38-99.25)	0.802

Parameters	Total (n = 331)	Interferon (n = 64)	Standard Care (n = 267)	p-value
≤ 50 U/liter — no. (%)	104 (42.79 %)	26 (45.62 %)	78 (41.94 %)	0.366
> 50 U/liter — no. (%)	139 (57.21 %)	31 (54.38 %)	108 (58.06 %)	
Lactate Dehydrogenase (LDH) (U/liter) - median (IQR)	444.5(301-687.5)	578(383–845)	428(283.5–643)	0.398
≤ 245 U/liter — no. (%)	18 (15.25 %)	3 (9.09 %)	15 (17.65 %)	0.193
> 245 U/liter — 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/liter) - median (IQR)	1.3 (1-1.6)	1.1 (1-1.475)	1.3 (1.1–1.7)	0.412

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
Mortality earlier (Hospitalization ≤ 7 days) - no. (%)	72 (64.86 %)	14 (70 %)	58 (63.74 %)	0.348
Mortality later (Hospitalization > 7 days) - no. (%)	39 (35.14 %)	6 (30 %)	33 (36.26 %)	0.014
Hospital stay — median no. of days (IQR)	4 (2–7)	7 (5–9)	4 (2–7)	< 0.001
Respiratory factors				
Oxygen Saturation (SpO2) — median (IQR)	52.7 (36.9-80.58)	68.0 (42.25–88.65)	51.1(36.8–78.9)	0.153
PH (DISS) - median (IQR)	7.41 (7.32–7.46)	7.42 (7.34–7.47)	7.4 (7.32–7.46)	0.454
PaCO2 (DISS) - median (IQR)	30.5 (38.05–46.3)	38.2 (29.75–56.15)	37.2 (30.5–46)	0.593
PaO2 (DISS) - median (IQR)	36.3 (26.8–50)	36.3 (27–43)	36.3 (26.6–50.3)	0.581
HCO3(DISS) - median (IQR)	24.25 (21.28–26.9)	25.9 (22.4–27.2)	24 (21-26.8)	0.196
Respiratory rate	18.0 (17–22)	18.0 (16-18.75)	19 (17–23)	0.267
White Blood Cell count ($\times 10^{-9}$/liter) - median (IQR)	7.35 (5.3-10.28)	9.52 (7.03–12.68)	6.91 (5.3–9.8)	0.042
< 4 $\times 10^{-9}$/liter — no. (%)	10 (9.26 %)	1 (5 %)	9 (10.23 %)	0.257
4–10 $\times 10^{-9}$/liter — no. (%)	70 (64.81 %)	11 (55 %)	59 (67.04 %)	
> 10 $\times 10^{-9}$/liter— no. (%)	28 (25.93 %)	8 (40 %)	20 (22.73 %)	
Lymphocyte count ($\times 10^{-9}$/liter) - median (IQR)	0.88(0.66–1.24)	0.84 (0.68–1.25)	0.9 (0.62–1.2)	.0322
≥ 1.0 $\times 10^{-9}$/liter — no. (%)	42 (38.89 %)	7 (35 %)	35 (39.77 %)	0.449
< 1.0 $\times 10^{-9}$/liter — no. (%)	66 (61.11 %)	13 (65 %)	53 (60.23 %)	

Parameters	*Total (n = 331)*	*Interferon (n = 64)*	*Standard Care (n = 267)*	*p-value*
Platelet count ($\times 10^{-9}$/liter) - median (IQR)	176 (138.5-223.75)	205(171-235.25)	170 (133.5–218)	0.204
$\geq 100 \times 10^{-9}$/liter — no. (%)	103 (95.37 %)	20 (100 %)	83 (94.32 %)	0.351
$< 100 \times 10^{-9}$/liter — no. (%)	5 (4.63 %)	0 (0 %)	5 (5.68 %)	
Neutrophil count ($\times 10^{-9}$/liter) - median (IQR)	5.89 (3.77–8.72)	8.3 (5.01–10.64)	5.5 (3.6–8.3)	0.628
$< 1.5 \times 10^{-9}$/liter — no. (%)	3 (2.89 %)	1 (5 %)	2 (2.54 %)	0.041
1.5-8 $\times 10^{-9}$/liter — no. (%)	67 (64.42 %)	8 (40 %)	54 (68.35 %)	
$> 8 \times 10^{-9}$/liter — no. (%)	34 (32.69 %)	11 (55 %)	23 (29.11 %)	
C-Reactive Protein (CRP) - median (IQR)	55 (29.6–74.4)	45 (27.55–60.6)	56 (32.3-74.45)	0.37
CRP < 6 — no. (%)	2 (2.53 %)	0 (0 %)	2 (3.28 %)	0.594
CRP > 6 — no. (%)	77 (97.47 %)	18 (100 %)	59 (96.72 %)	
Erythrocyte Sedimentation Rate (ESR) - median (IQR)	49.5 (35-69.5)	45 (27.5–65)	52 (35–70)	0.411

From other clinical factors, the median of White Blood Cell count and Lymphocyte count were significantly different between Recigen group and controls. In addition, the distribution of Neutrophil count showed difference between two groups under study. Also we used logistic regression model to calculate the odds ratio of mortality for patients who just treated by standard care, compare to Recigen group. According to analysis in crude model, the Odds of death in control groups, compared to Recigen group was 1.13 (95% CI: 0.63–2.04, P.value = 0.67) and the adjusted OR (for Respiratory rate, saturation, and HCO3) was 1.13 (95% CI: 0.58–2.18, P.value = 0.71). Since the mortality was lower for 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 two groups; the crude OR was 3.96 (95% CI: 1.37–11.43, P.value = 0.011) as similar as the adjusted OR, which was 4.02(95% CI: 1.22–13.21, P.value = 0.022), which revealed that patients who treated with standards care and hospitalized for at least one week were at higher risk of death, compared to same patients who treated with Recigen.

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.

Mortality rate in severe COVID-19 patients was reported between 62–81 percent (16). Recent study showed COVId-19 patients with more severe disease had significantly decreased interferon activity and SARS-CoV-2 induced suppressed interferon-beta release was reported in vitro (17, 18). There are increased risk of severe lung disease in people with comorbidities, older age or who receiving immunosuppressive medication due to less interferon-beta production (19, 20).

Interferon beta is superior to other interferons in inhibition of coronaviruses replication (21). It should be used in early phase of viral infection to reach a protective effect and late application of interferon may exacerbate the disease (22, 23). IFN-beta increases CD73 which plays role in vascular integrity in hypoxic conditions (24). High serum level of interferon is needed to reach antiviral effect (23). Long term safety and tolerability of INF-beta are proven due to its application in multiple sclerosis treatment (25).

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

In previous randomized trial, combination of INF-B with lopinavir/ritonavir and ribavirin, was safe, alleviated the symptoms and shortened the duration of hospital stay compared with triple antiviral therapy alone (26).

in other trial, INF-beta significantly improved the discharge rate and lower the 28–day mortality, especially in patients who received in early phase of disease (27).

There were some kinds of limitations in this study. The most important limitation is that this study was conducted in the critical phase of 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, groups matching and homogeneity of the patients in the beginning of this outbreak. We entered limited numbers of COVID-19 patients to the study because of the restriction in COVID-19 PCR tests in Loghman Hakim hospital. Considering above limitations, we didn't design this study as a randomized clinical trial.

Conclusion

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

Declarations

Ethics approval and consent to participate: 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 .

Consent for publication: Yes

Availability of supporting data: Qualified researchers can submit proposals to the corresponding author with a valuable research question (with relevant approvals including ethical approval) to request access to any of the deidentified datasets of this clinical trial. A formal contract will be signed and an independent data protection agency should oversee the sharing process to ensure the safety of the participants data.

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Authors' contributions: M.F., I.A.D., and S.B. prepared the first draft. M.A.P. conducted the analysis on data and edited the first draft. M.G.B. and I.A.D. finalized all drafts, approved the final version of the manuscript, and made the decision to submit the results. S.S.N.I. conceived of the study and provided overall guidance. I.A.D., S.S., M.S., M.A., M.H., M.M., G.M., and M.Z. 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.

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