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Efficacy and safety of Interferon-beta 1a in the management of the outpatients with mild to moderate COVID-19 (A preliminary study)

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Abstract---Interferon-beta 1a (IFN β -1a) has been shown some promising effects on the management of severe COVID-19. We aimed to evaluate the efficacy and safety of IFN β -1a in patients with confirmed mild to moderate COVID-19. Respiratory rate (RR) and saturation oxygen (SpO₂) were considered as the primary objectives of the study. This cross-sectional randomized controlled clinical trial was conducted for 6 months. All patients received acetaminophen and an antihistamine for symptom relief as needed. Subjects in the intervention group received IFN β -1a (ReciGen®) 12 million units subcutaneously every other day for three doses. From 201 participants, 100 patients (49.8%) received IFN β -1a and 101 (50.2%) were included as the control group. The mean difference of SpO₂ between baseline and post-intervention was significantly higher in the intervention group compared to the control group (3.87% \pm 2.44% vs -0.59% \pm 1.38%; $p < 0.00$, respectively). Also, the reduction in the RR was significantly higher in patients who received IFN (-28.92% \pm 8.64% vs 0.51% \pm 7.54%; $p < 0.001$, respectively). No IFN-related adverse reactions were detected in our study except injection site reactions in 11 females and 7 males (18% of patients), characterized by erythema, edema, and pain. In conclusion, we revealed that early administration of IFN β -1a was effectively improved the clinical status (Both SpO₂ and RR) of the patients with mild to moderate COVID-19 without serious adverse reactions.

Keywords---COVID-19, Interferon beta, Mild to moderate disease, Clinical state, Outpatients.

Introduction

A novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has involved the world with coronavirus disease 2019 (COVID -19) pandemic since the end of 2019 (1-4). This disease is mainly characterized by a mild to severe respiratory illness but can affect different people in different ways that appear to be influenced by age, comorbidities, and genetic factors (5-7). The spectrum of the disease varies from asymptomatic infection to severe and critical pneumonia with acute respiratory distress syndrome (ARDS) and multiorgan injuries (1-3, 8). In approximately 80% of patients, the illness is mild and outpatient management is appropriate for them (3).

Several mechanisms have been proposed for the pathogenesis of the COVID-19 including the effect of the virus on interferons (IFNs) (1, 9). IFNs are a family of cytokines that are produced in the response to viral infections (8). The antiviral activities of type 1 IFNs (IFN-I), including IFN α and IFN β , are well known (1, 9-12). The evaluation of the patients with varying severity of COVID-19 showed that besides the decreased level of IFN-I in these patients, which was correlated with the severity of the disease, its function was also severely impaired (1, 11, 13). This IFN dysregulation highlights the potential of recombinant IFN-I proteins, both IFN α and IFN β , as a treatment option for patients with COVID-19 either as a

single agent or in combination with other antiviral agents due to its broad antiviral activities and anti-inflammatory properties (1, 10, 11).

To the best of our knowledge, the use of IFN β -1a in outpatients with mild to moderate COVID-19 has not been evaluated. This study aimed to evaluate the efficacy and safety of subcutaneous IFN β -1a in these patients.

Method

Study design

This cross-sectional randomized controlled clinical trial was conducted on patients with COVID-19 who were evaluated in Saghi clinic in Tehran, Iran, within 48 hours of the onset of their symptoms and categorized as mild to moderate by an infectious disease specialist based on severity classification of WHO (4). The protocol of the study was approved by the Institutional Review Boards of the Ethics Committee of SBMU (IR.SBMU.PHARMACY.REC.1400.080). And also was registered, reviewed, and approved by the Iranian Registry of Clinical Trials (IRCT), with the registry number IRCT20120703010178N25. The study began in January 2021 and was completed in July 2021.

Eligibility criteria

Inclusion criteria of the study were defined as patients with confirmed COVID-19, based on reverse transcriptase-polymerase chain reaction (rt-PCR) who had mild to moderate disease. Age younger than 18 years old, the onset of symptoms more than 48 hours, patients with severe to critical COVID-19, immunocompromised state, receiving any antiviral agent or glucocorticosteroid, liver enzymes more than 3 times higher than the normal range, psychologic disorders, platelet count below 50,000/dL, hemoglobin less than 10 g/dL, lactation and pregnancy were considered as not-inclusion criteria.

Sample size and randomization

To the best of our knowledge, this was the first study about the effect of IFNs in the outpatient setting, so we designed this study as a cross-sectional study with a period of 6 months. The randomization was performed by permuted block randomization and block sizes of 4 generated by the sealed envelope website (www.sealedenvelope.com).

Interventions

Patients were recruited based on defined inclusion and exclusion criteria and after signing the written informed consent form. Recruited patients were randomly divided into intervention and control groups with a ratio of 1:1. All patients received acetaminophen and an antihistamine for symptom relief as needed. Subjects in the intervention group received IFN β -1a (ReciGen®) 12 million units subcutaneously every other day for three doses.

Clinical information of enrolled patients including body temperature (T), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), pulse rate (PR), and level of oxygen saturation in the peripheral circulation (SpO₂) was evaluated at the beginning and 7th day of the study.

All patients were evaluated for IFN-related adverse reactions including nausea, vomiting, diarrhea, abdominal pain, and injection-related reactions like skin erythema and edema, fever, chills, headache, skeletal pain, and myalgia.

Outcome

The primary outcome of the study was the efficacy of IFN β -1a on the clinical status of the outpatients with confirmed mild to moderate COVID-19 based on RR and SpO₂. The safety of the treatment was also evaluated as a secondary outcome.

Statistical analysis

Data description for qualitative variables performed using frequency (percentage). For quantitative data, the description was performed by reporting mean \pm standard deviation (SD) or median (interquartile range (IQR)) for parametric and non-parametric data. To evaluate the distribution of the quantitative variable, the Kolmogorov-Smirnov test was used. To assess the differences in frequency of the qualitative data Chi² test or Fischer exact test (in time the frequency of more than 20% of the variables were less than 5) were used. To compare the differences of the quantitative data between the two groups, the independent sample t-test or Mann-Whitney U test were performed for data with normal or non-normal distribution, respectively. All statistics were performed using Statistical Package for the Social Sciences version 25 (SPSS, IBM Corp. Released 2017. IBM SPSS statistics for windows, Version 25. Armonk, NY: IBM Corp).

Results

From the total of 201 patients included in the study during 6 months, one hundred (49.8%) received IFN β -1a, and 101 (50.2%) were included as the control group. The median age of the included patients was 43 (19) years. Regarding the age variable, significant differences were observed between the two groups of the study (46.37 ± 13.76 vs 40.90 ± 14.28 , $p=0.006$ in the intervention and control arms of the study, respectively). Ninety-three subjects (46.3%) were male and 108 (53.7%) were female. But female - male ratio was not significantly different between 2 groups (53 (53%):47 (47%) vs 40 (39.6%):61 (60.4%), $p=0.057$ in the intervention and control groups, respectively).

According to the baseline clinical characteristics of the patients (Table 1), the RR was significantly higher in the intervention group (26.91 ± 3.21 vs 21.36 ± 3.42 , $p<0.001$). Also, the SpO₂ was significantly lower in the intervention arm of the study ($94.00(4.00)$ vs $97.00 (4.00)$, $p<0.001$). So, for baseline correction, the differences between post-intervention and baseline values were calculated for both evaluated parameters. The difference in SpO₂ was $3.87\% \pm 2.44\%$ in the intervention group and was $-0.59\% \pm 1.38\%$ in the control group that

demonstrates significant improvement in oxygen saturation in patients who received IFN β -1a ($p < 0.001$). Also, the reduction in the RR was significantly higher in patients who received interferon compared to the control group ($-28.92\% \pm 8.64\%$ vs $0.51\% \pm 7.54\%$, $p < 0.001$). Data related to post-intervention and differences (%) of the variables are presented in Table 1.

We did not detect any IFN-related adverse reactions except injection site reactions in 11 females and 7 males (8.9% of patients).

Discussion

We evaluated the efficacy of subcutaneous IFN β -1a on the outpatients with mild to moderate COVID-19 as the primary object. According to the WHO classification, mild to moderate COVID-19 is defined as no sign of severe pneumonia, SpO $_2 \geq 90\%$, and RR < 30 in adults with clinical signs of pneumonia (4). Although the disease was significantly more severe in the intervention group at the beginning of the study regarding both clinical parameters (RR and SpO $_2$), the improvement in clinical status was significantly higher among patients who received IFN β -1a compared to those who did not ($p < 0.001$ for both).

The antiviral activities of IFN-I are well known (1, 9-12). Some studies showed the superiority of IFN β over IFN α against viral infections (14). Also, the potential effect of the IFN β on decreasing virus-induced lung fibrosis (15) and reducing vascular leakage and mortality rate in patients with ARDS (16) can be helpful in the improvement of the outcomes among patients with severe COVID-19 who had ARDS.

The efficacy of the IFN β -1a on the management of COVID-19 was evaluated by some studies on patients with severe disease (8, 17-19). Davoudi ME. et al. reported the significant association between the early administration of IFN β -1a in patients with severe COVID-19 with an increased rate of discharge on day 14 and reduced 28-day overall mortality compared to the control group ($p = 0.015$). Alavi ID. et al. also showed a significantly lower time to clinical improvement among patients with severe COVID-19 who received IFN β -1a than the control group ($p = 0.031$) (18). Using IFN β -1a in combination with antiviral agents in patients with severe COVID-19 was also recommended by Payandemehr P. et al. (17) and Dastan F. et al (19). Emanuele B. et al identified IFN β -1a as a promising drug for COVID-19 to reduce the duration of hospital stay and improve the clinical status (20).

We included patients who were referred within 48 hours of the onset of the symptoms. Early administration of IFN β for the treatment of COVID-19 during the first 7 days of onset of the symptoms, viral phase, was associated with improved efficacy on controlling the viral replication and prevention of viral invasion to the tissue (21, 22), whereas starting the antivirals after the cytokines release phase significantly decreased their efficacy. It was also mentioned that prophylactic use of IFNs may block viral infection at the very early stage with cause a pre-existing antiviral state in target cells (1).

We detected no IFN-related adverse reactions in our study except injection site reactions in 11 females and 7 males (8.9% of patients), characterized by erythema, edema, and pain. The low prevalence of adverse reactions maybe because of the similarity between these reactions with the symptoms of the COVID-19 and receiving concomitant conservative treatments including acetaminophen and antihistamine that may mask the reactions. Davoudi ME. et al. detected some adverse effects including fever, chills, myalgia, and headache in 8 (19%) patients with severe COVID-19 who received IFN β -1a in few hours after injection of it that all of them were tolerable (8). No adverse drug reaction was reported for IFN β -1a in hospitalized patients with COVID-19 who received IFN in addition to other antiviral agents by Payandemehr P. et al. (17) and Dastan F. et al. (19).

The single-center experience, small sample size, lack of following the patients in terms of needing to hospital and/or ICU admission, absence of data about the comorbidities and other medications that patients were used concomitantly were the main limitations of our study. Considering the limitations of this study, a large-scale clinical trial is needed to confirm our findings.

Conclusion

We revealed that early administration of IFN β -1a was effective in significant improvement in the clinical status (Both SpO₂ and RR) of the patients with mild to moderate COVID-19

without serious adverse reactions.

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Conflict of Interests:

All authors declare no potential conflicts of interest for the research, authorship, and/or publication of this article.

Author contributions:

MH designed the study. Investigation and Drafting of the proposal were done by EP. MH and EP were involved in collecting data. OM, EP, and MS were analyzed data. Data interpretation and writing original draft preparation were done by OM, EP, and MS. EP and MS reviewed and edited the preparation. All authors helped to manuscript improvement and finalize the article for publication.

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Table 1. Baseline, Post-intervention, and differences (%) of the variables

Variable		Intervention Group (n=100)	Control Group (n=101)	p-Value
Temperature (°C)	Baseline	37.35 ± 0.58	37.25 ± 0.57	0.210
	Post-intervention	36.50 (0.00)	36.80 (1.00)	<0.001

	Difference (%)	-2.06 (2.27)	-1.07 (1.58)	<0.001
Systolic Blood Pressure (mmhg)	Baseline	103.40 ±10.17	106.19 ± 11.56	0.071
	Post-intervention	117.95 ± 10.49	109.60 ± 8.82	<0.001
	Difference (%)	10.00 (10.91)	0.00 (10.00)	<0.001
Diastolic Blood Pressure (mmhg)	Baseline	66.10 ± 7.90	67.82 ± 8.32	0.134
	Post-intervention	75.50 ± 6.72	70.99 ± 6.40	<0.001
	Difference (%)	16.67 (4.17)	0.00 (16.67)	<0.001
Oxygen Saturation (%)	Baseline	94.00 (4.00)	97.00 (4.00)	<0.001
	Post-intervention	98.00 (2.00)	97.00 (3.00)	<0.001
	Difference (%)	3.87 ± 2.44	-0.59 ± 1.38	<0.001
Pulse Rate (beats/min)	Baseline	97.68 ± 12.82	94.31 ± 14.29	0.080
	Post-intervention	82.25 ± 9.51	86.60 ± 10.75	0.003
	Difference (%)	-14.82 ± 11.89	-6.92 ± 12.57	<0.001
Respiratory Rate (Breath/min)	Baseline	26.91 ± 3.21	21.36 ± 3.42	<0.001
	Post-intervention	18.94 ± 1.90	21.39 ± 3.41	<0.001
	Difference (%)	-28.92 ± 8.64	0.51 ± 7.54	<0.001