Original Article

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The administration of Interferon-beta1b and favipiravir in patients with COVID-19 pneumonia

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Abstract

To assess the efficacy of interferon-beta1b (INF-beta1b) in combination with favipiravir in early treatment of patients with COVD-19 pneumonia. This prospective non-controlled study was performed on admitted patients with moderate to severe COVID-19 disease to Amir-Alam hospital. The diagnosis of COVID-19 pneumonia was based on positive RT-PCR test from nasopharyngeal samples and typical spiral chest CT scan findings. At the time of this study, there was the shortage of efficient anti-COVID drugs especially "Remdesivir" due to sanction of Iran. All the patients received subcutaneous IFN-beta1b plus favipiravir. The patients with severe infection received intravenous dexamethasone. Those who underwent invasive or noninvasive mechanical ventilation, at the admission onset, were excluded from the study. One hundred and eighty-two patients with moderate to severe COVID-19 pneumonia were included in this study. Among182 patients, 90 cases had moderate and 92 had severe pneumonia. Twenty-one cases with severe pneumonia and 14 cases with moderate pneumonia were transferred to ICU to receive invasive or non-invasive mechanical ventilation. The mean duration of hospital ward admission and ICU stay was 10.69±7.54 and 5.45±2.72 days, respectively. One hundred and seventy-four patients (80.7 %) recovered completely and discharged without need to ICU admission. The response rate was the same in patients with moderate and severe pneumonia. Nine cases (4.9 %) were passed away. Diabetic patients had higher mortality rates. This study showed the efficacy of IFN-beta1b plus favipiravir in early treatment of patients with moderate to severe COVID-19 pneumonia who did need to mechanical ventilation.

Keywords: COVID-19 pneumonia, Interferon-beta1b, Favipiravir, Treatment.

1. Introduction

COVID-19 is a worldwide problem with scares approved therapeutic options. It could present with a wide range of clinical manifestations from mild symptoms which recover without any medical intervention to severe pneumonia with significant mortality rates. According to the literatures, about 80% of patients with COVID-19 present with mild symptoms while remaining 20% require hospital admission with a mortality rate of 4% (1-3). The reported mortality rate of Covid-19 is higher among patients with coexisting medical conditions, including hypertension, diabetes, morbid obesity and cardiovascular diseases (4). Patients with moderate to severe COVID-19 disease need to receive appropriate medical treatment. Currently, there are only few drugs approved for

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COVID-19 disease with limited accessibility, especially in low resource areas. As a result, physicians empirically prescribe other available antiviral agents to inhibit the coronavirus replication.

Interferon beta (IFN-beta), a subgroup of type I interferon (IFN-I), is currently available in two forms of IFN-beta1a, and IFN-beta1b (5). IFN-beta has direct antiviral and immunomodulatory activities. It could overcome the ability of coronaviruses to escape immune recognition via suppression of IFN-type I expression (6). Two previous studies indicated the positive effect of INF-beta1a on COVID19 (7, 8). One another study showed the efficacy of IFN-beta1b in combination with two other antiviral agents on patients with mild to moderate COVID-19 (9).

In this prospective non-controlled study, we evaluate the efficacy of IFN-beta1b in combination with favipiravir in patients with moderate to severe Covid-19.

2. Materials and methods

This prospective non-controlled study was performed on admitted patients with moderate to severe COVID-19 disease to Amir-Alam hospital from 1th June to 31th August 2020. The diagnosis of COVID-19 pneumonia was based on positive RT-PCR test from nasopharyngeal samples to identify SARS-COV-2 infection and typical spiral chest CT scan findings including bilateral, subpleural, ground-glass opacities and consolidations. The patients with atypical chest CT scan findings or negative RT-PCR test were excluded from the study.

Our inclusion criteria were:

1. Patients with moderate to severe COVID-19 pneumonia.
2. Blood oxygen (O2) saturation of 93% or less while breathing room air.
3. The symptoms onset less than 7 days before admission.

The severe infection defined as blood O2 saturation < 90 mmHg while breathing room air.

The exclusion criteria were patients underwent invasive or noninvasive mechanical ventilation and those with concomitant mixed connective tissue diseases or history of organ transplantation.

Data were collected from questionnaires including demographic information and past medical history. The blood O2 saturation and vital signs were monitored at the beginning of admission and minimally two-times a day, thereafter.

At the time of study, there was shortage of efficient anti-COVID drugs especially "Remdesivir" because of sanction of Iran. All the patients received subcutaneous (SC) IFN-beta1b 0.25 mg (8 million international unit) every other day for maximum of 5 doses plus oral favipiravir 1600 mg two times a day in the first day followed by 400 mg three times a day for 4 days. The mentioned drug regimen was started as soon as the patient was admitted to hospital to maximize its efficacy. The supplementary oxygen was given by nasal cannula or mask with reservoir bag. The intravenous (IV) dexamethasone (4 mg two times a day) was prescribed for patients with severe infection defined as blood O2 saturation less than 90 mmHg. The patients were regularly monitored in terms of therapeutic efficacy. The primary therapeutic response was defined as increased in blood O2 saturation higher than 93 mmHg while breathing room air and decreased respiratory rate to less than 20 per minute. The secondary therapeutic response was defined as complete recovery and discharge from the hospital. The duration of hospitalization, need to ICU admission and final outcome were collected.

2.1. Informed consent

This study was performed in accordance with the Declaration of Helsinki and has received ethical approval from the ethical committee of Amir alam Hospital, Tehran University of Medical Sciences. Informed consent will be obtained from eligible patients or from the patient's legally representative. The ethics code number of IR.TUMS.AMIRALAM.REC.1399.037 was adopted by this study.

2.2. Statistical analysis

Descriptive statistics was used to describe the data. Frequencies and percentages were used to express categorical variables. Differences between groups were analyzed using Pearson's $\chi 2$ tests (or Fisher's exact tests for expected cells of <5). For

continuous variables, mean and standard deviation were used to summarize the data while analyses were performed using Student's t-test and Mann-Whitney test. Logistic regression analysis was applied to determine the factors that could be considered independent predictors of unfavorable clinical outcome. Statistical analysis was performed using SPSS version 16.1.

3. Result

In this study 182 patients with moderate to severe COVID-19 pneumonia, consist of 116 males and 66 females, with the mean age of 53.96 ±14.70 years (range from 21 to 91-year-old) were included. The diagnosis of COVID-19 was based on positive result of RT-PCR test and typical spiral chest CT-scan findings. Ninety cases had moderate and remaining 92 patients had severe pneumonia. The most common comorbid conditions were obesity [body mass index (BMI) equal or over 30] and diabetes mellitus (DM). Forty-nine cases (26.9 %) had DM. Sixty-two (34.1 %) patients had obesity and 80 (44 %) cases were overweight (25<BMI<30). Hypertension, cardiovascular and pulmonary diseases were less common comorbid conditions. Seventy-three cases had no important comorbidities. No significant differences were found between the severe and moderate patients with respect to gender, age, and comorbidities. (Table 1).

Among the total number of 182 patients, 21 cases with severe and 14 cases with moderate pneumonia were transferred to ICU to receive invasive or non-invasive mechanical ventilation. The mean duration of hospital ward admission and ICU stay was10.69±7.54 and 5.45±2.72 days, respectively. There were no notable differences in need to ICU admission and length of stay in ICU and ward between the moderate and severe groups. (Table 1).

According to logistic regression, DM had significant association with outcome. Univariate regression analysis was performed to assess the effect of patients' demographic characteristics and co-morbid conditions on COVID-19 outcome, which did not show any significant associations. DM (OR, 6.04; P=0.014) was identified as independent predictor of unfavorable outcome. (Table 2).

All cases received IFN-beta1b plus favipi-

Table 1. Demographic and clinical characteristics, signs and symptoms at presentation.

Variable, n (%) unless specified otherwise	All (N=182)	Moderate (N=90)	Severe(N=92)	P- value
Sex				
Male	116(63.7)	57(63.3)	59(64.1)	
Female	66(36.3)	33(36.7)	33(35.9)	0.911
Age	53.96±14.70	52.18±14.88	55.69±14.40	0.108
Comorbidity				
DM	49(26.9)	26(28.9)	23(25)	0.554
Obesity				
<25	40(22)	21(23.3)	19(20.7)	
25-30	80(44)	38(42.2)	42(45.4)	0.870
>30	62(34.1)	31(33.4)	31(33.7)	
DM+ Obesity	18(9.9)	37.43±0.77	37.23±0.78	0.194
Temperature at admission	37.26±0.78	10.43±2.55	10.95±10.32	0.641
Length of stay ward	10.69±7.54	6.21±3.01	4.95±2.45	0.184
Length of stay ICU	5.45±2.72			
Outcome		87(96.7)	86(93.5)	0.321
Discharge	173(95.1)	3(3.3)	6(6.5)	
Death	9(4.9)			

Table 2. The estimation of mortality odds ratio for study-specific variables Univariate.

Variable	Univariate		
	Odds ratio	**95%CI**	**P-value**
O2 saturation	1.091	0.993-1.2	**0.07**
Length of stay ward	0.971	0.921-1.07	**0.938**
Length of stay ICU	0.992	0.741-1.329	**0.959**
DM			
No	-	-	-
Yes	6.047	1.450-25.22	**0.014**
Obesity			
No	-	-	-
Yes	2.47	0.641-9.581	**0.188**

Significant level <0.05

ravir. Patients with severe pneumonia received IV dexamethasone. The response rate was not different between patients with moderate and severe pneumonia. One hundred and forty-seven patients recovered completely and discharged without need to ICU admission. Ultimately, 9 cases of 182 patients (4.9 %) were passed away.

4. Discussion

The devastating effects of COVID-19 pandemic on world's health, has made the issue a research priority, especially in finding appropriate treatment strategies. Currently, the only approved drug options are an antiviral agent with the name of "Remdesivir" as well as steroid components.

Remdesivir interferes with the replication of some viruses, including SARS-CoV-2. This drug was shown to shorten the hospital stay but had no significant effect on mortality rate (10). In the time of this study, remdesivir was not available in our country because of sanction. Considering the unavailability of remdesivir, other antiviral agents including oral atazanavir/r and favipiravir were added to IFN-beta1b in our treatment regimen.

Interferons are molecules produce naturally in reaction to viral infections. They could stimulate the immune system to attack the invaders, while avoid damaging the body's own tissues. Previous studies showed that the natural interferon response is suppressed in some patients with COVID-19. *In vitro* research showed that interferon type1 can inhibit SARS-CoV-2 and two closely related viruses, SARS-CoV and MERS-CoV (11-14).

One study evaluated the effect of IFN-beta1b plus lopinavir-ritonavir plus ribavirin on mild to moderate COVID-19. They found that this triple combination strategy was associated with shortening the duration of virus shedding, alleviating symptoms and facilitating the discharge of patients with mild to moderate COVID-19 (9).

Another study suggested that it is wise to start IFN-beta early in the course of disease because its immunomodulatory effect maximize in the early stages of COVID-19 (15).

According to another study, severely ill COVID-19 patients with increased levels of plasma cytokines (especially IL-6) showed signs of immune exhaustion and poor IFN responses (16). Even such cases may benefit from IFN-beta. INF-beta can induce a desired immune boost, simultaneously downregulate IL-6 and IL-8 (17) and prevent extravasation of neutrophils into lungs (18). In contrary, the result of another study showed that IFN-beta1a was not effective in treatment of critical patients who developed ARDS (19).

Favipiravir, is an anti-viral drug originally designed for influenza. This drug has a similar mechanism of action to remdesivir and emerging as an agent that is worth considering in mild to moderate COVID-19 cases (20, 21). As with any antiviral agent, it is recommended that favipiravir should be administered early after the onset of symptoms for maximal efficacy in reducing viremia.

In this study, Interferon-beta1b plus an oral favipiravir showed acceptable efficacy on moderate to severe COVID-19 pneumonia with the response rate of approximately 95%.

In this study, both moderate and severe groups showed similar response rate. We presumed that adding IV dexamethasone to severe patients' drug regimen could play a role in mentioned unexpected favorable response. Dexamethasone and other steroids are potent anti-inflammatory drugs which is available and inexpensive. Many physicians have prescribed steroids for critically ill COVID-19 patients. There are evidences that steroids are effective in patients with hyper-immune response to viral infection. The most striking effect of dexamethasone was reported in critically ill patients with mechanical ventilation. However, in patients who receive oxygenation without mechanical ventilation, steroids could reduce the mortality rate by 20% (22).

Several previous studies reported different in-hospital mortality rate of COVID-19 patients. In a study, out of 41 admitted hospital patients, 13 cases (32%) were admitted to ICU and six patients (14•6%) died (23). Another study, on 138 hospitalized patients with COVID-19, 26% of patients required ICU admission and 4.3% died (24). In another retrospective cohort study in France, the in-hospital mortality rate of 89530 patients with COVID-19 were reported as16•9% (25). Compare to the results of mentioned studies, our in-hospital mortality and need to ICU admission were relatively low . The median hospital-stay in our patients was 10.69±7.54 days. The JAMA study found that, among patients discharged from hospital, the median hospital-stay was 10 days (24).

This study has some limitations. Due to our limited access to extensive drug choices and the urgent medical condition, it was not feasible to include a control group to our study. Our study was performed on patients with early stages of infection. It is suggested to evaluate the efficacy of interferon-beta1b in advance stages of disease, in future research.

In conclusion, this prospective study showed the efficacy of IFN-beta1b plus favipiravir in early treatment of moderate to severe COVID-19 pneumonia.

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Conflict of Interest

None declared.

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