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International Immunopharmacology 92 (2021) 107329

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Combination therapy of IFNβ1 with lopinavir–ritonavir, increases oxygenation, survival and discharging of sever COVID-19 infected inpatients

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ARTICLE INFO

Keywords:
Covid-19
IFN-β1-a
Survival
Intensive care
Outcome
Mortality

ABSTRACT

Interferon Beta-1a (IFN-β1-a), an immunomodulatory mediator with antiviral effects, has shown in vivo and in vitro activities especially on coronavirus including SARS-CoV-2. COVID-19 defined as the disease caused by infection with SARS-CoV-2. The virus has been illustrated inhibits the production of IFN-β1-a from inflammatory cells. We conducted a retrospective study of all adult confirmed COVID-19 hospitalized patients who received combination of three doses of 12 million international units of IFN-β1-a and Lopinavir 400 mg and Ritonavir 100 mg every 12 h (case group) for 14 days besides standard care and age- and sex- matched COVID-19 patients with receiving lopinavir/ritonavir (control group) at Masih Daneshvari Hospital as a designated hospital for COVID-19 between Feb 19 and Apr 30, 2020. Multivariate analysis was done to determine the impact of IFN-β1-a on outcome and all-cause mortality. 152 cases in IFN-β1-a group and 304 cases as control group were included. IFN-β1-a group stayed at hospital longer and required noninvasive ventilation more than control group (13 vs. 6 days, $p = 0.001$) and (34% vs. 24%, $p = 0.04$), respectively. During treatment, 57 (12.5%) patients died. The death rate in case and control groups was 11% and 13% respectively. In multivariate analysis, not receiving IFN-β1-a (HR 5.12, 95% CI: 2.77–9.45), comorbidity (HR 2.28, 95% CI: 1.13–4.60) and noninvasive ventilation (HR 2.77, 95% CI: 1.56–4.93) remained significantly associated with all-cause mortality. In this study, risk of death decreased by using IFN-β1-a in COVID-19 patients. More clinical study will be necessary to measure efficacy of IFN-β1-a in COVID-19 treatment.

1. Introduction

COVID-19, the infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become an overwhelming and worldwide dilemma of health care system since Dec 2019 [1,2]. The virus transmitted promptly by person to person and has various symptoms from asymptomatic to respiratory failure and eventually death [3–5]. In addition, it has shown cytokine storm by increasing uncontrolled cytokines such as interleukin 6 (IL-6) in some cases however; there is no specific treatment or antiviral agents to suppress virus and consequent inflammation [6]. Antiviral defense especially interferon (IFN) release system can be inhibited by viruses such as SARS and

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https://doi.org/10.1016/j.intimp.2020.107329
Received 17 August 2020; Received in revised form 16 November 2020; Accepted 19 December 2020
Available online 26 December 2020

Middle East respiratory syndrome coronavirus (MERS-CoV) [7]. On the other hand, type I IFN may reduce as a consequence of a generalized immunosuppression induced by high viral load [8]. It is shown that IFNs' circulation is not detectable in infected patients such as COVID-19 [9]. Moreover, severe and critical patients displayed lower activity and diminished response of type ɪ IFN compared to mild to moderate patients [9]. Thus usage IFN can be effective in antiviral immunity. Among IFNs, type I IFN particularly IFNβ was utilized for treatment coronavirus in different studies and had various results. In general IFNβ is a more powerful inhibitor of coronavirus than IFNα [10,11]. At present, few clinical trials suggest usage IFNβ on treatment and controlling COVID-19 in the world [12].

Current treatment includes oxygen support, antibiotics, some unproved antiviral drugs, anti-inflammatory compounds and immunoglobulin. Lopinavir and ritonavir and interferon beta (IFN-β) have been shown to have efficient activity on serious adverse events (respiratory failure or death) of SARS and MERS-CoV [13,14] and have improved pulmonary function [15]. Iran has got involved in COVID-19 extensively in Middle East Region in Asia [16]. As many countries, COVID-19 was a new storm for clinicians in Iran however we had an experience with H1N1 [17]. Finding efficient medication with considering previous experience is a moral duty of clinicians and researchers. In this report, we illustrated outcomes in a nested case-control study of patients admitted for COVID-19 with or without using IFN-β1-a in a referral center in Tehran, Iran.

2. Material and methods

2.1. Study design and population

A retrospective (a nested case-control) study of confirmed patients with COVID-19 infected was carried out at Masih Daneshvari Hospital from Feb 19 toApr 30, 2020. All patients with any symptoms suggestive for COVID-19 were admitted at Masih Daneshvari Hospital in Tehran, Iran. This hospital is a National Research Institute of Tuberculosis and Lung Disease (NRITLD) but, in this situation of country with in view of experiment in China, it is designed as a referral center for suspected cases of coronavirus. A throat swab was taken from the patients for COVID-19. These respiratory samples were the same type and were done in our referral virology lab. A diagnosis of COVID-19 was confirmed by a positive reverse- transcriptase-polymerase-chain- reaction (RT-PCR) for coronavirus with extraction of nucleic acid from the samples with the QiaSymphony system (QIAGEN, Hilden, Germany). Corman et al has described the process of detection of coronavirus using primer and probe sequences for screening and conformation [18].

Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total and direct bilirubin), urea and creatinine were measured for all patients. Other additional baseline evaluation was requested if deemed necessary by physicians. Patients are monitored for adverse drug reactions based on clinical symptoms and signs. The study protocol was approved by Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.NRITLD.REC.1398.102). The registration number of this trial registered in Iranian Registry of Clinical Trials is IRCT20151227025726N12.

2.2. Patient selection

We included all adult confirmed COVID-19 patients who received three to five doses of IFN-β1-a (ReciGen®, CinnaGen, Iran) 12 million international units (44 μg) subcutaneous injection on alternate days (during five days) at the beginning of admission at hospital and lopinavir 400 mg plus ritonavir 100 mg twice a day for 14 days with standard careas cases [19]. The cases were received IFN-β1-a if they were adult (age $\geq$ 18 years), had a positive RT-PCR of the throat swab for COVID-19, and severe disease. Respiratory rate $\geq$ 30 breaths/min or an oxygen saturation (Sao_2) $\leq$ 90%in room air or a partial pressure of arterial oxygen to percentage of inspired oxygen ratio (PaO2/FiO2) of $\leq$ 300 was considered as a severe disease. We excluded the patients with a history of allergy to IFN, other causes of lower respiratory infection such as viruses, bacteria, fungal and receiving less than three doses of IFN. We randomly selected in a 1:2ratio age- and sex-matched control with lopinavir and ritonavir regimen without using any type of IFN. Supportive treatment such as antipyretic, antibiotics, serum therapy and supplemental oxygen by nasal or mask as needed on clinician's discretion is provided. For both cases and controls, all patients had a diagnostic positive RT-PCR for COVID-19 with a chest imaging compatible to coronavirus infection and had a Sao_2 92% or less while breathing ambient air. In addition, we adjusted dose of lopinavir plus ritonavir in the cases who had treatment-emergent increase in serum ALT greater than five times the upper limit of normal. All cases or their legally authorized representative must have signed informed consent form.

All patients could be discharged if they had a negative RT-PCR, a $Sao_2 \geq$ 93% in ambient air for 15 min, and no fever for in last 24 h.

2.3. Data collection and outcomes

We abstracted demographic and clinical information from patient records. The primary study outcomes were improvement of oxygen requirement, survival, and all-cause mortality. We defined improvement as a Sao_2more than 93% while breathing ambient air in sitting position. When the patients were in improvement situation, we discharged them with health care recommendation such as wearing mask, hand hygiene frequently, at least two meter distance of other people and improving airflow at home.

2.4. Data analysis

We compared categorical variables using the chi-squared or Fisher's exact test and non-normally distributed continuous variables using the Mann Whitney *U* test. Multivariate logistic regression adjusting for age and gender was done to determine whether using IFN-β1-a was independently associated with survival or improvement of oxygen requirement. Other predictors in the model entered if they were associated with survival or improvement of oxygen support and IFN-β1-a in bivariate analysis at $p < 0.2$. Kaplan-Meier survival analysis was used to examine the relationship between IFN-β1-a and treatment outcome (all-cause mortality) and survival curves using log-rank test were compared during days at hospital. Additionally, we performed Cox proportional hazards modeling adjusting for age and gender to determine whether not using IFN-β1-a was an independent risk factor for mortality and developing to invasive ventilation. Diabetes and other comorbidities are known to impact outcomes therefore they were considered as predictors [20,21].

These data were single entered, double checked into SPSS version 16.00 [SPSS Inc, Chicago, IL, USA]. All records were checked for completeness, reliability and precision.

3. Results

During the study period, 152 cases received the full three doses of IFN-β1-a plus lopinavir and ritonavir and 304 age- and sex-matched as control who received lopinavir and ritonavir alone, were included in the analysis. The median days stayed in hospital was 13 (inter-quartile range [IQR] 5–37) and 6 (IQR 2–28) days among IFN-β1-a group and controls group respectively. Table 1 shows demographic and clinical characteristics of both groups. 68% of total patients were male gender and the median age was 56 years (IQR, 44–66). At baseline, patients in control group were more likely to receive invasive ventilation (74 vs. 51, $p = 0.036$) and patients receiving invasive had a tendency to be older (61 years, vs. 54 years, $p < 0.001$), lymphopenia (61% vs. 39%, $p = 0.023$), more concomitant (73% vs. 47%, $p < 0.001$), including chronic renal failure (6% vs. 1%, $p = 0.006$), hypertension (38% vs. 22%, $p < 0.001$), DM (31% vs. 17%, $p = 0.001$). There were 57 deaths, including 17

Table 1
Baseline demographics of COVID-19 study patients.

Characteristics	IFN-β1-a group N = 152	Control group N = 304	p-value
Age	56 (18–94)	56 (18–92)	1
Male gender	104 (68%)	208 (68%)	1
Days stayed in hospital	13 (5–37)	6 (2–28)	<0.001
Duration of symptoms	7 (2–15)	7 (0–30)	0.4
Co-diseases			
Diabetes	36 (23.7%)	59 (19.4%)	0.2
Hypertension	41 (27%)	77 (25.3%)	
Ischemic heart disease	25 (16.4%)	47 (15.5%)	
Hypothyroidism	4 (2.6%)	12 (4%)	
Cancer	5 (3.3%)	7 (2.3%)	
Lung disease	13 (8.5%)	23 (7.5%)	
Rheumatoid arthritis	3 (2%)	2 (0.6%)	
Chronic renal failure	5 (3.3%)	5 (21.6%)	
Obesity	11 (7.2%)	24 (8%)	
Smoker	3 (2%)	9 (3%)	
other	2 (1.3%)	11 (3.6%)	
White blood cell	6400	5870	0.7
Lymphocyte count	960	1187	0.2
AST (U/L)	40	37.5	0.4
ALT (U/L)	33	26	0.4
Bilirubin total (mg/dL)	0.8	0.6	0.07
LDH (Ul/L)	627	487	0.007
Cr (mg/dL)	1.10	1.15	0.7
Fasting blood sugar (mg/dL)	162	136.5	0.2
Blood sugar (mg/dL)	167	187	0.05
Interlukin 6 (pg/mL)	3.9	12.6	0.08
Saturation O_2 (%)	87.1 ± 8.6	87.4 ± 7.3	0.9
CT scan (ground glass)			
unilateral	2 (1%)	14 (5%)	0.1
bilateral	150 (99%)	290 (95%)	
ICU admission	51 (41%)	74 (59%)	0.04
Outcome			
Discharge	135 (89%)	264 (87%)	0.50
Death	17 (11%)	40 (13%)	

AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, Cr; creatinine ICU; intensive care unite.

(11%) patients in IFN-β1-a group and 40 (13%) patients in control group. The most common symptoms were cough (98%), dyspnea (95%) and fever (91%) followed by headache (47%), myalgia (38%), anosmia (21%), ageusia (20%) and other symptoms (Table 2).

There is no significant difference between IFN-β1-a group and control group in mortality rate statistically although IFN-β1-a group had less mortality than controls group with considering of oxygen support significantly ($p < 0.001$) (Table 3).

In binary multivariate logistic regression the death rate was 3 times higher in control group besides co-disease and noninvasive ventilation requirement (Table 4). After adjusting for age, gender, and DM, noninvasive ventilation requirement (HR 2.80, $p = 0.001$, co-disease (HR 2.30, $p = 0.021$), and regimen without interferon B1a (HR 5.12, $p = 0.001$) remained independently associated with mortality. The cumulative incidence of mortality at 35 days at hospital was higher in control group (Fig. 1).

Table 2
Symptoms of COVID-19 study patients.

Characteristics	IFN-β1-a group N = 152 (%)	Control group N = 304 (%)	p-value
Cough	150 (98.7)	298 (98)	0.72
Fever	141 (92.8)	274 (90)	0.35
Dyspnea	145 (95.4)	290 (95.4)	1
Hemoptysis	5 (3.3)	1 (0.3)	**0.017**
Diarrhea	12 (7.9)	36 (11.8)	0.2
Nausea	20 (13.2)	37 (12.2)	0.76
Vomiting	15 (9.9)	23 (7.6)	0.4
Abdominal pain	15 (9.9)	50 (16.4)	0.06
Myalgia	76 (50)	96 (31.6)	**<0.001**
Sore throat	1 (0.7)	5 (1.6)	0.67
Headache	62 (40.8)	151 (49.7)	0.07
Runny nose	2 (1.3)	1 (0.3)	0.26
Anosmia	19 (12.5)	75 (24.7)	**0.002**
Ageusia	22 (14.5)	71 (23.4)	**0.026**

Table 3
Number of patients based on oxygen support requirement.

		Ambient air (N = 331)	Noninvasive ventilation(N = 65)	Invasive ventilation(N = 60)
+ IFN-β1-a	Death	0	14 (41.2)	3 (17.6)
	Discharged	101 (100)	20 (58.8)	14 (82.4)
− IFN-β1-a	Death	5 (2.2)	17 (54.8)	18 (42)
	Discharged	225 (97.8)	14 (45.2)	25 (58)
Improvement (discharge)		326 (98.5)	34 (52)	39 (65)

Table 4
Factors associated with outcome (all-cause mortality).

	Unadjusted OR (95%CI)	Adjusted OR (95% CI)
Control group*	2.50 (1.18–5.30)	5.12 (2.77–9.45)
Co-disease	3.31 (1.44–7.60)	2.28 (1.13–4.60)
Noninvasive ventilation	13.25 (6.53–26.90)	2.77 (1.56–4.93)

CI; confidence interval, OR; odds ratio.
* Not receiving IFN-β1-a.

4. Discussion

The present study shows that the regimen including IFN-β1-a and lopinavir plus ritonavir resulted in good prognosis and lower risk of mortality among COVID-19 patients. IFN-β1-a can reduce mortality rate at least five times besides noninvasive ventilation and comorbidity. Also, IFN-β1-a can improve oxygen support.

Several studies reported interferon as an efficient drug in SARS, MERS,and Ebola and recently for COVID-19 especially in combination with a nuclease inhibitor (ribavirin) or with a protease inhibitor (lopinavir/ritonavir). They have suggested using this combination in early onset of disease for clinical improving they mentioned association between these medication and their critical situation with mortality [14,22–24]. Clementi and colleagues demonstrated in vitro antiviral activity of IFN-β1-b on infected cells. Also, they showed that IFN-β1-a effectively inhibits virus replication and decreases viral RNA on treated cells [25]. Other studies had various results in the treatment of COVID-19 by interferon type I, including interferon alfa and beta [26,27]. A multicenter randomized trial compared a triple combination of IFN-β1-b, lopinavir/ritonavir, and ribavirin with lopinavir/ritonavir alone. They reported that the combination therapy was more effective in suppressing the virus shedding, clinical improvement with mild side effects, and duration of hospital stay [23]. In another randomized clinical trial, the efficacy of IFN-β1-b was evaluated. IFN-β1-b (250 μg every other day for two weeks) was added to lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine as their national protocol regimen.The control group was on the national protocol regimen. A statistically significant clinical improvement was seen in IFN-β1-b group with a remarkable reduction of mechanical ventilation and ICU admission [28]. Most of these studies were focused on the evaluation of IFN-β1-b in treatment of COVID-19. We evaluated IFN-β1-afor this purpose. We found combination of IFN-β1-a and lopinavir/ritonavir is more efficient with considering of oxygen support in survival and discharging the patients with a normal Sao_2than lopinavir/ritonavir alone. This result supports other study that it showed SARS-CoV-2 is more susceptible to type I interferon than SARS [23,29,30].

There are various results evaluating efficacy of lopinavir/ritonavir alone or in combination with interferon on outcome of treatment. In a recent trial has been shown lopinavir/ritonavir was not efficient in

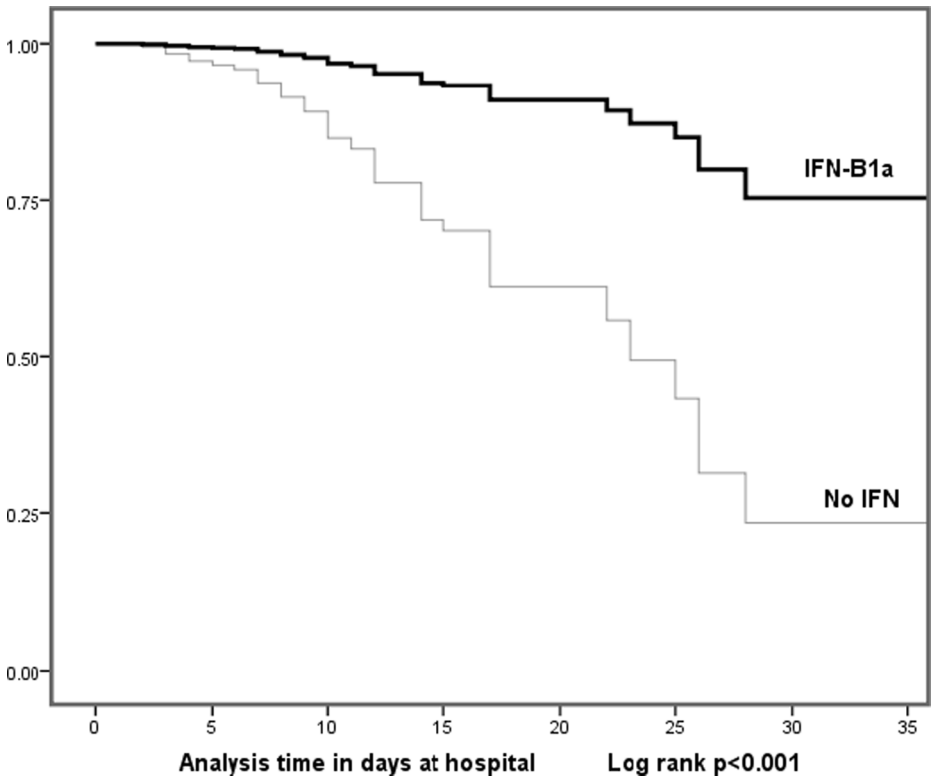

Fig. 1. Survival COVID-19 patients with or without IFN-β1-a.

treating COVID-19 that it might be due to late recruitment (median 14 days vs. 7 days) [31]. Our study have confirmed this finding of higher rates of all-cause mortalityin control group except that median days at hospital in IFN-β1-a group was more than control groups (13 vs. 6 days). It could be due to disease severity and more comorbidity in IFN-β1-a group that it is caused to stay at hospital more than control group. Additionally, the patients should be stayed at hospital for injection of IFN-β1-a at least 6 to 10 days.

In present study, all-cause mortality was more common among control group. Duration of symptoms was not significantly different between two groups, so the higher mortality rate in patients who received IFN-β1-a. The high rate of mortality may possibly be related to have comorbidities and to need noninvasive and invasive ventilation in control group. On the other hand, we could not perform autopsies in our center; consequently, we cannot exclude unrelated death to COVID-19. Besides, this center was a referral center for COVID-19 in pandemic situation.

Major strength of our study is the evaluation of COVID-19 treatment with IFN-β1-a and comparison to a relevant control group selected at random from the same study base. As many other studies, this report has some limitations. Our center was one of designated hospital for COVID-19, so partly; this finding may not be representative of all setting. Nevertheless, it is more likely that COVID-19 patients treated in other hospitals with less expertise and facilities would have even worse treatment outcomes. Second, we did not consider efficacy of IFN-β1-a in suppressing the shedding of SARS-CoV-2 because of the lack of adequate devices for doing PCR. In addition, we did not evaluate other concomitant medications in both groups as a cofounder factor. Finally, we could not perform another nasopharyngeal sample whether we achieved a negative sample as an improvement sign. We discharged the patients if they had Sao_2more than 93% while breathing ambient air not a negative RT-PCR for SARS-CoV-2.

In summary, this study emphasizes and confirms the similar studies for using interferon beta 1a with lopinavir/ritonavir to achieve best therapy for COVID-19. Severe or critically ill patients who need invasive ventilation or intensive care can be treated with IFN-β1-a in combination with other antiviral agents.

Funding Sources

None.

CRediT authorship contribution statement

Parvaneh Baghaei: Methodology, Data curation, Formal analysis, Investigation, Writing - original draft. **Farzaneh Dastan:** Resources, Validation. **Majid Marjani:** Resources, Investigation. **Afshin Moniri:** Resources, Investigation. **Zahra Abtahian:** Resources, Investigation. **Somayeh Ghadimi:** Investigation, Writing - original draft. **Melika Valizadeh:** Investigation, Writing - original draft. **Jalal Heshmatnia:** Writing - review & editing. **Maryam Sadat Mirenayat:** Writing - review & editing. **Atefeh Abedini:** Writing - review & editing. **Arda Kiani:** Writing - review & editing. **Alireza Eslaminejad:** Writing - review & editing. **Seyed MohammadReza Hashemian:** Writing - review & editing. **Hamidreza Jamaati:** Writing - review & editing, Project administration. **Alireza Zali:** Conceptualization, Visualization, Project administration. **Ali Akbar Velayati:** Conceptualization, Visualization, Project administration. **Payam Tabarsi:** Conceptualization, Visualization, Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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