Efficacy and Safety of Interferon Beta-1b in the Management of Patients with COVID-19: A Prospective, Open-Label, Non-Randomized Trial

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Background: There is no proven therapy for coronavirus disease 2019 (COVID-19) so far. The aim of this study was to evaluate the effect of interferon beta-1b combined with lopinavir/ritonavir and hydroxychloroquine in managing COVID-19.

Methods: This is a non-randomized, open-label study on adult patients with moderate to severe COVID-19. The patients (≥ 18 years) received hydroxychloroquine 400 mg single dose, and lopinavir 400 mg/ritonavir 100 mg every 12 h (for 7-10 days) with or without subcutaneous interferon (IFN) beta-1b 250 mcg every other day for three doses. The primary outcome was clinical improvement in NEWS2 changes. Duration of hospital stay, mortality rate, and safety profile of therapeutic regimens were secondary outcomes.

Results: Between March 20 and April 3, 2020, a total of 114 patients were recruited and 59 patients completed the study. The IFN group had a significant improvement in clinical symptoms due to a significant reduction in NEWS2 (83.3% (25) vs 48.3% (14), P= 0.004). The time to clinical response in the IFN group was shorter than the control group (7 (5-12) days vs 9.5 (7-18), P=0.037). The IFN group also showed a significantly lower rate of 28-day mortality (6.8% (2) vs 34.5% (10), P= 0.01) and a lower need for invasive ventilation (6.8% (2) vs 34.5% (10), P= 0.008). Although the duration of ICU stay was marginally shorter in the IFN group, the results were not significantly different between the two groups (P=0.06).

Conclusion: IFN beta-1b could be a potential therapeutic option for patients with moderate to severe COVID-19.

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Introduction
In December 2019, a novel coronavirus (SARS-CoV-2) was identified in Wuhan, China. The disease was called COVID-19 by the World Health Organization in February 2020. To date, more than 200 million people have been reported with the disease, and more than 4 million people...
have died from the disease (1). Most people with COVID-19 will experience mild to moderate symptoms and recover without special treatment. In a subset of patients, the virus causes severe acute respiratory syndrome (SARS), which is a major global public health concern (2).

It seems that the systemic disease caused by COVID-19 infection has two distinct but overlapping stages, including viral pathogenicity and host immune system response. Through concentrating viral replication, the earlier stage of infection results in exaggerated host immune responses, which could lead to severe consequences such as acute respiratory distress syndrome (ARDS) and multiple organ failure (3-5). Depending on the stage, different therapeutic agents can be considered. Early administration of pharmacological agents against the viral phase could have a great impact on controlling the disease, while anti-inflammatory/ immunosuppressant therapeutic regimens are more effective in the second phase.

Remdesivir, a nucleotide analogue (6), is currently the only therapy with uncertain efficacy approved for patients hospitalized due to severe COVID-19 (7). Besides, dexamethasone, a corticosteroid (8), has shown promising effects on survival improvement of clinically severe patients. However, the definite therapeutic intervention for COVID-19 has not been discovered yet. Since developing new therapeutic agents requires a long time, finding new applications for existing medications is a reasonable alternative, especially in the current pandemic (9).

Previous studies have demonstrated that coronaviruses are susceptible to IFN treatment (10, 11). Given the effects of recombinant IFNs (IFN-α, IFN-β, and exogenous IFNs) on SARS-CoV-2 and the Middle East respiratory syndrome (MERS)-CoV, IFNs appear to have an inhibitory effect on protein production and proliferation of viruses (12). As noted, the immunomodulatory effect of IFNs is also beneficial in patients with exaggerated immune response as in severe COVID-19 infection (13). An in-vitro study on the therapeutic effects of IFNs found that IFN β was the most effective IFN, which means it could be administered as an antiviral agent against SARS-CoV-2 (11). Moreover, when the treatment starts before and immediately after infection, it might have prophylactic effects as a result of inhibiting virus replication (5). In this context, we performed this study to evaluate the efficacy and safety of IFN β1-b for SARS-CoV-2-infected patients.

**Methods**

This open label, and non-randomized controlled clinical trial was conducted on COVID-19 patients admitted to Ibn e Sina Teaching Hospital, Sari, Iran. This study follows the declaration of Helsinki. It was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1399.005) and registered at the Iranian Registry of Clinical Trials (IRCT 20190804044429N1). An informed consent form was obtained from all patients or their legal representatives. All patients admitted between March and April, 2020, were screened and recruited consecutively. Using a 1:1 ratio, we allocated the participants to the intervention and control groups.

Adult patients were eligible for study if they were at least 18 years old and had confirmed or highly probable diagnosis of COVID-19 according to reverse transcriptase polymerase-chain reaction (RT-PCR), computerized tomography (CT) scan, and clinical symptoms. The last item included oxygen saturation ≤ 93% (Spo2) on ambient air or respiratory rate ≥ 24/ minute, in addition to one of the followings: body temperature ≥ 37.8 °C, cough (with or without sputum), dyspnea, fatigue, anorexia, and symptoms duration less than 10 days from recruitment. Patients were excluded if they had renal and hepatic failure, thyroid disorder, untreated severe depression, history of seizure, and allergy to any drugs of the therapeutic regimen; they were also excluded in case of pregnancy or breastfeeding.

According to the national guideline at the time of the study, all patients in the control group received a single dose of hydroxychloroquine (400 mg) and lopinavir/ritonavir (200/50 mg); specifically, they took two tablets twice daily for at least 5 days. In the intervention group, patients were given the standard therapeutic regimen in addition to subcutaneous IFN beta-1b (Ziferon®, Zistdaru Danesh, Iran) 250 mcg (8 million international unit) every other day for at least three doses. Before IFN administration, all patients received acetaminophen 325 mg and naproxen 500 mg as premedication regimen to prevent flu-like symptoms of IFN beta-1b.

Besides antiviral regimen, all patients received oxygen therapy with nasal cannula, non-invasive or mechanical ventilation support, antibiotic agents, and corticosteroids— if clinically indicated.

Clinical data related to vital signs, physical examinations, radiologic assessments, and safety profile were regularly recorded. We used the National Early Warning Score (NEWS2) to monitor clinical symptoms (Table 1) during the study (14). Accordingly, patients scoring more than 4 indicate moderate disease, and those scoring ≥ 7 indicate severe disease. Chest CT scan and electrocardiogram (ECG), complete blood count, lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver and renal function tests, troponin, and serum electrolytes were considered at baseline and monitored regularly until patient discharge. Blood, sputum, and urinary samples intended for bacterial or fungal culture were taken with respect to clinical indications.
Table 1. The NEWS2 scoring system.

| Parameters                          | Scores | Parameters                          | Scores |
|-------------------------------------|--------|-------------------------------------|--------|
| Respiratory rate (per minute)       | ≤ 8    | 2                                   | 9-11   |
|                                     |         | 1                                   | 12-20  |
|                                     |         | 0                                   | 21-24  |
|                                     |         | 3                                   | ≥ 25   |
| O₂ saturation 1 (%)                 | ≤ 91   | 92-93                              | 94-95  |
|                                     |         | ≥ 96                                |        |
| O₂ saturation 2 (%)                 | ≤ 83   | 84-85                              | 86-87  |
|                                     |         | 88-92                              | 93-94 on oxygen |
|                                     |         | 95-96 on oxygen                     | ≥ 97 on oxygen |
| Air/oxygen                          | Oxygen | Air                                |        |
| Systolic blood pressure (mm Hg)     | ≤ 90   | 91-100                             | 101-110|
|                                     |         | 111-219                            |        |
| Pulse rate (per minute)             | ≤ 40   | 41-50                              | 51-90  |
|                                     |         | 91-110                             | 111-130|
|                                     |         | ≥ 131                              |        |
| Consciousness                       | Alert  | CVPU                               |        |
| Temperature (°C)                    | ≤ 35   | 35.1-36                            | 36.1-38|
|                                     |         | 38.1-39                            | ≥ 39.1 |

CVPU: Confusion, Voice, Pain, Unresponsive

The primary outcome of the study was improvement in patients’ clinical symptoms based on NEWS2 changes. The scoring system included 6 physiologic parameters, each scored from 0 to 3; the higher the score, the further from the normal state (Table 1). The total score of 0-1 was considered as the clinical response, which was assessed in the two groups at intervals of 1-7, 8-14, and more than 14 days of treatment. The secondary outcomes were duration of hospital stay, need for intensive care (e.g., ICU admission, mechanical ventilation), and antiviral regimen tolerability. The safety concerns of the therapeutic regimens were assessed daily during the study period. The reported adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology study (15). All patients were followed up for one month.

Continuous variables were presented as mean or median, and categorical variables were expressed in frequency (percentage). To compare the quantitative variables between the two groups, we ran the independent sample t-test or Mann-Whitney test (for non-normally distributed variables). Chi-square test or Fisher’s exact test was used for qualitative variables. Generalized estimating equations (GEE) method was used to assess the effect of time and combination therapy with IFN beta 1b on NEWS2 changes. Multivariate analysis was performed and hazard ratios (HRs) were analyzed at a confidence interval of 95%; this was achieved by using Cox proportional regression model to evaluate the association between variables and duration of hospital stay. P-values less than 0.05 were considered statistically significant. All analyses were performed in SPSS-24.

By considering a difference of 4 days in time to clinical response and power of 85%, we estimated the sample size at 56 patients using the following equation:

\[
an = \frac{z_{1-\alpha}^2 \cdot \sigma^2}{\delta^2} \quad \sigma_1 = \sigma_2 = 5 \quad \delta = 4 \quad z_{1-\alpha/2} = 1.96 \quad z_{1-\beta} = 1.04
\]

Results
Overall, we screened 114 patients who had been admitted to the hospital with COVID-19 diagnosis. Sixty-four patients were recruited, and 32 patients were assigned to each study group according to the inclusion criteria. Two patients in the IFN group and three patients in the control group were excluded due to their unwillingness to continue the study. Finally, 59 patients completed the study and were analyzed.

Figure 1. Trial diagram.
The mean age of participants was 63 years old (±15), and 55% (32) of patients were male. There were no significant differences in the demographic and clinical characteristics of participants in the two groups at baseline. The most common clinical presentations of patients were fever, unproductive cough, and dyspnea (Table 2).

Notably, hypertension (44%) and diabetes mellitus (39%) were the most common underlying diseases in the patients. Besides the antiviral therapeutic regimens, ceftriaxone (89.8%), azithromycin (68%), doxycycline (37%), meropenem (52%), and vancomycin (43%) were administered as concomitant antibiotic treatment (Table 2).

Table 2. Demographics and baseline clinical characteristics.

| Parameters          | Interferon group (N=30) | Control group (N=29) | P-value |
|---------------------|-------------------------|----------------------|---------|
| Age (yr), mean (SD) | 65.09 (13.51)           | 60.79 (16.81)        | 0.277   |
| Sex                 |                         |                      |         |
| Male, n (%)         | 15 (50%)                | 16 (55.2%)           | 0.782   |
| Female, n (%)       | 15 (50%)                | 13 (44.8%)           |         |
| BMI, mean (SD)      | 27.66 (4.52)            | 27.87 (5.51)         | 0.869   |
| Smoking, n (%)      | 3 (9.7)                 | 0                    | 0.086   |
| Addiction           | 3 (9.7)                 | 4 (13.8)             | 0.62    |
| Comorbidities       |                         |                      |         |
| DM, n (%)           | 13 (41.9)               | 10 (34.5)            | 0.553   |
| HTN, n (%)          | 13 (41.9)               | 13 (44.8)            | 0.821   |
| DLP, n (%)          | 6 (19.4)                | 8 (27.6)             | 0.451   |
| IHD, n (%)          | 3 (9.7)                 | 6 (20.7)             | 0.233   |
| Malignancy, n (%)   | 2 (6.5)                 | 0                    | 0.164   |
| Stroke, n (%)       | 3 (9.7)                 | 0                    | 0.238   |
| Thyroid disorder, n (%) | 1 (3.2)     | 3 (10.3)             | 0.346   |
| Depression, n (%)   | 0                       | 2 (6.9)              | 0.229   |
| Asthma, n (%)       | 4 (12.9)                | 0                    | 0.113   |
| IBD, n (%)          | 1 (3.2)                 | 0                    | 0.321   |
| RA, n (%)           | 2 (6.5)                 | 0                    | 0.157   |
| AD, n (%)           | 2 (6.5)                 | 1 (3.4)              | 0.525   |
| At least one comorbidity, n (%) | 26 (86.7) | 18 (62)              | 0.03    |
### Baseline clinical symptoms

| Symptom               | Group 1 | Group 2 | p-value |
|-----------------------|---------|---------|---------|
| Fever, n (%)          | 10 (32) | 16 (55) |         |
| Chilling, n (%)       | 1 (3)   | 5 (17)  |         |
| Cough, n (%)          | 16 (53) | 19 (66) |         |
| Chest pain, n (%)     | 1 (3)   | 0       |         |
| Dyspnea, n (%)        | 15 (50) | 18 (62) |         |
| Fatigue, n (%)        | 3 (10)  | 7 (24)  |         |
| Headache, n (%)       | 4 (13)  | 1 (3)   |         |
| Muscle pain, n (%)    | 6 (20)  | 7 (24)  |         |
| Dizziness, n (%)      | 5 (17)  | 0       |         |
| Dyspepsia, n (%)      | 5 (17)  | 6 (21)  |         |
| Diarrhea, n (%)       | 1 (3)   | 1 (3)   |         |
| Nausea, n (%)         | 3 (10)  | 5 (17)  |         |
| Loss of appetite, n (%)| 5 (17) | 2 (7)   |         |
| Anosmia, n (%)        | 4 (13)  | 0       |         |
| Ageusia, n (%)        | 3 (10)  | 0       |         |
| NEWS2                 | 4 (0-6) | 4 (1-8) | 0.141   |

### Baseline lab tests

| Test            | Group 1    | Group 2    | p-value |
|-----------------|------------|------------|---------|
| AST             | 30 (14-160)| 34 (9-1963)| 0.969   |
| ALT             | 25 (8-79)  | 21.5 (0-1563)| 0.317  |
| N/L, , mean (SD)| 3.8 (2.15)| 8.3 (15.2) | 0.039   |
| *Hb             | 11.8 (9-17)| 11 (6.2-16.1)| 0.476  |
| *Plt            | 235 (0-554)| 185 (99-1065)| 0.730  |
| CRP, mean (SD)  | 1.1 (0.22) | 1.1 (0.34) | 0.805   |
| Cr, mean (SD)   | 1.1 (0.22) | 1.12 (0.35) | 0.805   |

* Values shown by median (minimum-maximum). BMI: Body Mass Index, DM: Diabetes Mellitus, HTN: Hypertension, DLP: Dyslipidemia, IHD: Ischemic Heart Disease, IBD: Irritable Bowel Disease, RA: Rheumatoid Arthritis, AD: Alzheimer Disease, NEWS2: National Early Warning Score, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, N/L: Neutrophil/Lymphocyte ratio, Hb: Hemoglobin, Plt: Platelets, CRP: C-reactive protein, Cr: Creatinine.
The rate of NEWS2 reduction, as an improvement of clinical symptoms, was compared between the two study groups. On the third, fifth, and seventh days of hospitalization, NEWS2 changes in the two groups were significantly different, such that the IFN group showed a better trend of clinical improvement on these three days (P-values: 0.003, 0.003, and 0.005, Table 3). The overall trend of this change during the first seven days of hospitalization was significant in the IFN group (P-value: 0.006, Figure 2, Table 4). Moreover, 25 patients in the IFN group and 14 patients in the control group demonstrated clinical response, which was significantly different (P-value: 0.004, Table 3). According to the GEE model, the trend of NEWS2 changes in the two groups was significantly different with the effect size of -1.045, confirming that the intervention has, on average, reduced NEWS2 by 1 unit.

Duration of hospital stay in the IFN group was 1 day less than the other group, but the difference was not statistically different (Table 3).

Also, 5 (16.7%) patients in the IFN group and 11 (37.9%) patients in the control group were admitted to ICU. However, no significant differences occurred between the two groups in terms of the need for ICU admission and ICU stay days (P-values: 0.112, 0.06). In addition, 10 patients in the control group required invasive ventilation, which suggested a significantly higher rate than that in the IFN group (P-value: 0.008, Table 3). Mortality occurred for 12 patients, including 2 patients in the IFN group and 10 patients in the control group, showing a significantly lower rate in the IFN group (P-value: 0.01, Table 3).

According to multivariate analysis, administration of special therapeutic agents including angiotensin-converting enzyme, angiotensin receptor blockers, statins, azithromycin, doxycycline, and naproxen with possible beneficial effects on COVID-19 showed no significant effects on clinical response (Table 5).

The most common side effects in the study groups were mild and tolerable and did not interfere with continuing treatment (Table 6).
Table 5. Multivariable analysis of concomitant medications effects on clinical response.

| Drug                | Multivariable OR (95% CI) | P-value |
|---------------------|---------------------------|---------|
| Naproxen            | 0.315 (0.065-1.518)       | 0.15    |
| Statin              | 1.245 (0.282-5.503)       | 0.77    |
| Statin              | 0.258 (0.043-1.564)       | 0.14    |
| Azithromycin        | 0.743 (0.202-2.733)       | 0.65    |
| Azithromycin        | 0.15 (0.02-0.50)          | 0.13    |
| Doxycycline         | 0.614 (0.179-2.104)       | 0.44    |

OR: odd ratio, ACEi/ARBs: Angiotensin Converting Enzyme/Angiotensin II Receptor Blockers.

Table 6. Adverse drug reactions.

| Adverse drug reactions | Control (n=29) | IFN (n=30) | P-value |
|------------------------|----------------|------------|---------|
| Constipation, n(%)     | 6 (20.7)       | 2 (6.6)    | 0.116   |
| Tachycardia, n(%)      | 5 (17.2)       | 2 (6.6)    | 0.209   |
| Nausea, n(%)           | 8 (27.6)       | 15 (50)    | 0.078   |
| Vomiting, n(%)         | 4 (13.8)       | 2 (6.6)    | 0.365   |
| Headache, n(%)         | 1 (3.4)        | 2 (6.6)    | 0.574   |
| Increased liver enzymes, n(%) | 0     | 2 (6.6)    | 0.492   |

Discussion

Our study showed that, compared to lopinavir/ritonavir and hydroxychloroquine alone, IFN beta-1b administration in combination with lopinavir/ritonavir and hydroxychloroquine can be an effective therapeutic approach in patients with moderate to severe COVID-19. This is supported by the fact that the combination therapy led to a significant reduction in NEWS2 during hospital stay (as shown by patients’ clinical response), significant reduction in 28-day mortality rate, a lower need for an invasive strategy to improve oxygenation. The results of monitoring safety concerns indicated that most of the reported adverse effects were mild and tolerable.

Viruses are able to resist antiviral agents which, due to the high rate of genomic mutation, target vital components of their protein structures (16). From the physio-pathological point of view, in COVID-19 patients, the imbalanced immune response is manifested by reduced levels of IFN type I and III and increased levels of various inflammatory cytokines (17, 18). The ability of IFNs to modulate the immune system and antiviral activity (16) can be deployed alongside other antiviral agents with various mechanisms to combat viral infections.

Recently, two clinical trials have shown the potential benefit of combining IFN beta 1b with different antiviral agents to fight SARS-CoV2 infection. An open-label and randomized clinical trial on 66 patients with severe COVID-19 substantiated that the combination of IFN beta 1b with lopinavir/ritonavir and hydroxychloroquine was more effective than administering only lopinavir/ritonavir and hydroxychloroquine therapy to shorten clinical symptom time and reduce the need for ICU admission. The authors in that research administered IFN beta 1b for two consecutive weeks. The overall mortality, ICU stay, and during of hospitalization were not significant among the study groups (19). In compare to our study, IFN was administered at same dose for longer duration and clinical improvement was defined as two-grade decrease on the six-category ordinal scale. The results of time to clinical response, hospital stay, ICU admission and duration was consistent with our findings. Although, we achieved significant effects of IFN on mortality rate and need of intubation, our study sample size did not have enough power to differentiate the effects of study intervention on these variables.

Similarly, a multicenter, open-label, randomized clinical trial on patients with mild to moderate COVID-19 demonstrated that early treatment with combination therapy of lopinavir/ritonavir, ribavirin and IFN beta-1b had comparable effects on the time to negative RT-PCR of nasopharyngeal samples (as primary outcome) (20). IFN was administered for 3 doses during hospital stay. No death was reported, and hospital complications were not comparable to our study. This variation could be related to the stage of the patients’ disease in that study (mild to moderate), which differed from our study. Also, because of resource limitations, we were not capable of reporting viral clearance in sample patients. Similar to our results, the time to clinical response was significantly more favorable in the IFN group than in the control group. It may be inferred that adopting IFN combination therapy in early stages of SARS-CoV2 infection, mainly caused by the virus itself (5), can amplify the success of the antiviral regimen.

One of the most important concerns over combination therapy regimens is related to their safety profile and patient tolerability. In our study, the majority of the reported side effects were mild to moderate, and they rarely necessitated treatment discontinuation. In the IFN group, we were worried that flu-like symptoms could exacerbate patients’ conditions. However, administering naproxen and acetaminophen as premedication helped control the symptoms and, hence, no complaints were reported in this group.

The limitations of this non-randomized and open-label study include its small sample size and no determination of the virological response. Besides, the nature of the study design (non-randomized and open label) was another limitation prompted by the emergency situation at the time of the study. Moreover, at the time of the study we did not have access to recommended therapeutic agents such
as remdesivir and the beneficial effects of dexamethasone were not known. Therefore, it is necessary to carry out larger randomized clinical trials on COVID-19 patients through a combination of different therapeutic agents; this should be according to possible synergistic antiviral effects to make a more definite recommendation about effective antiviral regimens.

Totally, our findings showed that IFN beta-1b combined with lopinavir/ritonavir and hydroxychloroquine has an acceptable safety profile and could be a more beneficial therapeutic regimen compared to lopinavir/ritonavir and hydroxychloroquine alone. Consequently, it is proposed as a potential therapeutic option for patients with moderate to severe COVID-19.

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