Subcutaneous injection of interferon-α2b for COVID-19: an observational study

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Abstract

Background

The global pandemic of coronavirus disease 2019 (COVID-19) infection is ongoing and associated with high mortality.

Objective

The aim of this study was to investigate the efficacy and safety of subcutaneous injection of interferon-α2b (IFN-α2b) combined with lopinavir/ritonavir (LPV/r) in the treatment of COVID-19 infection, compared with that of using LPV/r alone.

Methods

Patients diagnosed with laboratory-confirmed COVID-19 infection in Wuhan Red Cross hospital during the period from January 23, 2020 to March 19, 2020 were included. The length of stay, the time to viral clearance and adverse reactions during hospitalization were compared between patients using oral LPV/r and combined therapy of LPV/r and subcutaneous injection of IFN-α2b.

Results

A total of 22 patients were treated with LPV/r alone and 19 with combined therapy with subcutaneous injection of IFN-α2b. The average length of hospitalization in the combination group (16 ± 9.7 days) was shorter than that of LPV/r group (23±10.5 days). Moreover, the days of hospitalization in early intervention group decreased from 25 ± 8.5 days to 10 ± 2.9 days compared with delayed intervention group. Combined therapy with IFN-α2b also significantly reduced the duration of detectable virus in the upper respiratory tract. No patient in each group was transferred to intensive care unit (ICU) or died during the treatment. There was no significant difference in the adverse effect composition between two groups.

Conclusion

Subcutaneous injection of IFN-α2b combined with LPV/r might shorten the length of hospitalization and accelerate viral clearance in COVID-19 patients, which deserves further investigation in clinical practice.

Introduction

Since December 2019, large numbers of patients were diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections worldwide, also known as coronavirus disease 2019 (COVID-19),
with a rapid growth rate exceeding that of "severe acute respiratory syndrome" in 2003. As of June 10, 2020, over 7 million COVID-19 cases and 406,668 deaths have been confirmed globally. SARS-CoV-2 infection can lead to intensive care unit (ICU) admission and high mortality [1]. It is still a challenge to effectively shorten the duration of viral shedding and the length of hospitalization, so as to avoid a run on local medical resources, reduce the occurrence of severe complications and improve the recovery rate. In the absence of a SARS-CoV-2 specific vaccine, effective antiviral therapy is an important part.

Type I interferons have broad spectrum antiviral activities against RNA viruses, which are usually used to treat hepatitis, though it is reported to inhibit SARS-CoV reproduction in vitro [2]. According to the seventh edition of the Chinese Guidelines, in addition to oral medication such as lopinavir/ritonavir (LPV/r) and ribavirin, vapor inhalation of IFN-α may be considered. Clinical trials have been registered to test whether therapeutic regimens of IFN-α2b combined with LPV/r can be beneficial for the treatment of COVID-19. However, the specific method for administration of IFN-α is vapor inhalation at a dose of 5 million U (and 2 mL of sterile water for injection) for adults, 2 times/day [3, 4]. The aerosols produced during treatment with atomized IFN-α are also exhaled, influencing its efficacy. Moreover, whether vapor inhalation of the medication has a systemic therapeutic effect remains unclear.

Herein, we performed a retrospective cohort study in patients with confirmed COVID-19 on the efficacy and safety of subcutaneous injection of IFN-α2b combined with LPV/r, compared with that of using LPV/r alone.

**Methods**

**Subjects and study design**

The research protocol of this single-center, retrospective cohort study conformed to the principles of the Declaration of Helsinki and was approved by the institutional ethics board of West China Hospital of Sichuan University (No.2020-126). Written informed consent was collected from all patients. Patients diagnosed with laboratory-confirmed COVID-19 infection in Wuhan Red Cross hospital during the period from January 23, 2020 to March 19, 2020 were included. Nasopharyngeal swabs of upper respiratory tract were collected from all patients, and patients enrolled in this study were diagnosed according to the following criteria based on WHO recommendation: isolation of COVID-19 or at least two positive results by real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) assay for COVID-19 or a genetic sequence that matched COVID-19 [5]. Eligible patients were those aged 18 years or older. Patients who were intubated, who died, or who were transferred to another hospital within 24 hours after admission were excluded. Patients receiving oral LPV/r were classified as LPV/r group, while those given LPV/r and subcutaneous injection of IFN-α2b were divided into combination group.

**Procedures**

Treatments during the epidemic were empirical. All eligible patients rested in bed in the isolation wards and daily sufficient caloric intake, balance of water-electrolyte and stability of internal environment were
ensured. Oxygen therapy was given according to each patient’s oxygen saturation. Antibiotics were only administered in patients with combined bacterial infection. For anti-viral treatment, LPV/r group were given oral lopinavir/ritonavir tablets (Abb-Vie Ltd, North Chicago, IL, USA; 200mg/50mg/ pill), 400 mg/time, twice a day, and combination group were supplemented with subcutaneous injection of IFN α-2b (3SBIO Inc, Shenyang, China; 3 million IU/ dose), 3 million IU/time, qod, in the basis of LPV/r treatment. The course of LPV/r treatment was 10 days, while IFN was used until the virus was detected negative by RT-PCR in two consecutive respiratory specimens (≥ 1 day apart). In addition to regular clinical monitoring (body temperature, respiratory rate, blood pressure, pulse, symptoms and signs), blood count, liver enzymes and renal function were assessed at baseline and throughout the treatment course. Two investigators (B.W. and Y.L.) obtained all clinical information, including demographic data, medical history, co-morbidities symptoms, signs, laboratory findings and management from electronic medical records of Wuhan Red-cross Hospital.

**Outcome measurements**

The primary outcomes were the length of hospitalization and the time to viral clearance of SARS-CoV-2 in the upper respiratory tract from hospital admission. The secondary outcomes included adverse effects, ICU admission rate, and hospital mortality during the treatment.

**Statistical analysis**

Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as counts and percentages. Means for continuous variables were compared using independent t test when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using the χ2 test or Fisher-Exact test when appropriate. Time to viral clearance, defined as the days from hospital admission to the first negative PCR of two negative consecutive PCR tests, was portrayed by Kaplan-Meier plot and compared with a log-rank test. P < 0.05 was considered statistically significant. All statistical analyses were performed by SPSS 25.0 for Windows (IBM, Chicago, IL, USA).

**Results**

**Patient characteristics**

A total of 41 patients older than 18 years fulfilling the WHO criteria of SARS-CoV-2 infection were enrolled in this study. The average age was 60.6 years and 18 (43.9%) were male. 24 patients had one or more coexisting medical conditions, including hypertension, diabetes, hepatitis and malignancy. 22 patients received oral LPV/r only and 19 were given combined therapy of oral LPV/r and subcutaneous injection of IFN-α2b. Baseline characteristics including age, gender, comorbidities, and time from onset to admission were generally similar between the two groups (P > 0.05; Table 1).

**Primary outcomes**
The average length of hospitalization was 20 days (range 5–45). As shown in Figure 1, the average length of hospitalization in combination group (16±9.7 days) was significantly shorter than that of LPV/r group (23±10.5 days) ($P<0.05$). Further comparison was conducted between early intervention (within 72 hours of admission) and delayed intervention (after 72 hours of admission) with IFN-α2b, which indicated that the days of hospitalization in early intervention group decreased from 25±8.5 days to 10±2.9 days compared with delayed intervention group ($P<0.05$). As shown in Figure 2, assessing the time to viral clearance, the data revealed a significantly accelerated viral clearance in patients receiving combined therapy of oral LPV/r and subcutaneous injection of IFN-α2b ($P<0.05$).

Secondary outcomes

Transient fever (maximum at 38.0 °C) and digestive upsets were present in 4 and 11 patients, respectively. 6 patients showed decreased white blood cell count, while 11 patients had elevated transaminase. No patient in each group was transferred to ICU or died during the treatment. There was no significant difference in the adverse effect composition between two groups ($P>0.05$; Table 2). All adverse effects were alleviated after symptomatic treatment, and no anti-viral treatment was discontinued.

Discussion

By inducing an antiviral response across a wide range of cell types and mediating adaptive immune response, type I IFNs can interfere with the replication and spread of virus [6]. Clinically, type I IFNs have already been approved for use in the treatment of viral infections (hepatitis B and hepatitis C), autoimmune disorders and certain cancers. Importantly, treatment of type I IFNs has been studied against SARS-CoV and MERS-CoV in numerous in vitro and in vivo experiments, in combination with or not with lopinavir/ritonavir, ribavirin and corticosteroids [7–9]. The knowledge gained from these studies may be valuable in the selection of potential treatments against SARS-CoV-2, since MERS-CoV and SARS-CoV share some similar properties with SARS-CoV-2 [10]. SARS-CoV-2 displays in vitro a substantial sensitivity to IFN-α pretreatment, implying that IFN-α might be used as a prophylaxis against SARS-CoV-2 [11].

More recently, analyses have suggested that inhaled IFN-α2b accelerated viral clearance from the respiratory tract and hastened resolution of systemic inflammatory processes when compared to arbidol treatment alone [12]. The administration of IFN-α2b by vapor inhalation may offer the advantage of targeting specifically the respiratory tract, but the pharmacodynamics and pharmacokinetics of this mode need further assessment. Notably, SARS-CoV-2 has been observed to have an organotropism beyond the respiratory tract, including the kidneys, liver, heart, and brain, which could possibly influence the course of COVID-19 disease and aggravate preexisting conditions [13]. Systemic therapeutic effect of vapor inhalation of IFN-α2b remains unclear. Besides, vapor inhalation may also promote the formation of aerosols, increasing the risk of aerosol transmission of virus in a relatively closed environment.

On the contrary, the subcutaneous and intravenous modes of administration have been well-described and already proven safe in several clinical trials. However, the efficacy and safety of subcutaneous
injection of IFN-α have not been evaluated in SARS-CoV-2 infection. In current study, we found that subcutaneous administration of IFN-α2b appeared to shorten the length of hospitalization and the duration of viral shedding. Moreover, among 11 patients who received IFN-α2b within 72 hours of admission, the average length of stay was 10 days, which was far shorter than that of patients given IFN-α2b after 72 hours of admission. These results were consistent with previous studies on MERS-CoV showing that a delay in starting treatment was associated with worse outcomes [14], suggesting that earlier subcutaneous injection of IFN-α2b may be associated with a higher efficacy in the treatment of SARS-CoV-2 infection. In addition, our study found that supplementary of IFN-α2b was adequately tolerated and no new safety concerns were identified. The overall proportion of patients with adverse events were similar between two groups.

Our study has several limitations due to the small sample size and its retrospective, nonrandomized nature. Meanwhile, it impossible to show any association between temporal viral load changes and antiviral therapy due to the absence of serial viral load measurement in upper and lower respiratory tract specimens. Besides, although baseline characteristics of the two groups seem to be balanced, impact of other confounders on the course of COVID-19 disease should be reassessed in larger cohorts. Selection and unmeasured confounding bias cannot be excluded. Therefore, we could not easily draw an accurate conclusion about the role of IFN-α2b in patients with COVID-19 by now.

Taken together, our clinical experience and available descriptive data from the therapeutic process are prone to support subcutaneous injection of IFN-α2b for specific subgroup of COVID-19 patients. However, large-scale randomized controlled trials are needed to look at the effectiveness, as well as the appropriate dosages and timing of subcutaneous injection of IFN-α2b in COVID-19.

Abbreviations

COVID-19: coronavirus disease 2019, IFN-α2b: interferon-α2b, LPV/r: lopinavir/ritonavir, ICU: intensive care unit, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, RT-PCR: real-time reverse-transcription-polymerase-chain-reaction, SD: standard deviation

Declarations

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Author Contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Wang Bo, Li Diandian, Luo Fengming and Liu Yanbin. The first draft of the manuscript was written by Wang Bo and Li Diandian. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1. Baseline characteristics of patients with COVID-19

|                                | LPV/r group | Combination group | \( P \)- value |
|--------------------------------|-------------|-------------------|---------------|
| Age, year (mean±SD)            | 62.0±9.4    | 56.2±9.7          | 0.058         |
| Male, n (%)                    | 8 (36)      | 10 (53)           | 0.295         |
| Days from symptom onset to hospital admission (mean±SD) | 11±6.8 | 12±7.3 | 0.214 |
| Coexisting medical conditions, n (%) |          |                   |               |
| Hypertension                   | 5 (22.7)    | 4 (21.1)          | 1.000         |
| Diabetes                       | 5 (22.7)    | 6 (31.6)          | 0.524         |
| Hepatitis                      | 1 (4.5)     | 0 (0)             | 1.000         |
| Malignancy                     | 1 (4.5)     | 2 (10.5)          | 0.895         |
| Symptoms, n (%)                |             |                   |               |
| Cough                          | 13 (59)     | 10 (52.6)         | 0.678         |
| Shortness of breath            | 6 (27.3)    | 4 (21.1)          | 0.922         |
| Pharyngalgia                   | 2 (9)       | 4 (21.1)          | 0.524         |
| Arthralgia/myalgia             | 7 (31.8)    | 4 (21.1)          | 0.438         |
| Chest pain                     | 4 (18.2)    | 2 (10.5)          | 0.804         |
| Fatigue                        | 7 (31.8)    | 9 (47.4)          | 0.309         |
Table 2. Adverse effects in patients with COVID-19 by patient group

| Adverse Effect                  | LPV/r group | Combination group | P-value |
|--------------------------------|-------------|-------------------|---------|
| Decreased white blood cell count, n (%) | 3 (13.6)    | 3 (15.8)          | 1.000   |
| Elevated transaminase, n (%)    | 6 (27.3)    | 5 (26.3)          | 0.945   |
| Mild anemia, n (%)              | 2 (9)       | 0 (0)             | 0.490   |
| Transient fever, n (%)          | 1 (4.5)     | 3 (15.8)          | 0.495   |
| Digestive upsets, n (%)         | 6 (27.3)    | 5 (26.3)          | 0.945   |

Figures
Figure 1

Comparison of length of hospitalization among patients with COVID-19 by patient group. Confirmed COVID-19 patients were treated with oral LPV/r alone or combined therapy of subcutaneous IFN-α2b injection and oral LPV/r. For combination group, patients who received IFN-α2b within 72 hours of admission were defined as the early intervention group, while those who received IFN-α2b after 72 hours of admission were defined as the delayed intervention group. Data are expressed as mean ± SD.
Figure 2

Subcutaneous injection of IFN-α2b accelerated viral clearance. Time to viral clearance of SARS-CoV-2 by RT-PCR among patients with COVID-19 by patient group.