

Comparative therapeutic efficacy of interferon and combination Kaletra plus interferon alpha-2b against SARS-CoV-2

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Abstract

Background: The outbreak of coronavirus disease 2019 (COVID-19) posed an enormous threat to public health. The use of antiviral drugs in patients with this disease have triggered people's attentions. Whether interferon alfa-2b or Kaletra plus interferon alfa-2b treatment can against SARS-CoV-2 was unknown. **Methods:** This is a retrospective cohort study of 123 laboratory-confirmed COVID-19 patients between Jan.13 2020 and Apr. 23. All patients received standard supportive care and regular clinical monitoring, patients were assigned to standard care group (n=12), interferon alfa-2b group (n=44), and combination Kaletra plus interferon alfa-2b group (n=67) according to their therapies. The primary endpoint was the duration of oxygen-support requirement and virus clearance time. The associations of therapies with these outcomes were assessed by Cox proportional hazards regression. **Results:** Baseline clinical characteristics were similar among 3 groups ($p < 0.05$). There was no significant associations of Kaletra /interferon alfa-2b with faster SARS-CoV-2 RNA clearance (HR, 0.85 [95% CI, 0.45–1.61]; $P = 0.61$ in interferon alfa-2b group vs HR, 0.59 [95% CI, 0.32–1.11]; $P = 0.10$ in Kaletra plus interferon alfa-2b group). The duration of oxygen-support requirement in therapy groups similarly showed no significant associations. There were no differences among 3 groups in the incidence of adverse events ($p < 0.05$). **Conclusions:** In patients with confirmed SARS-CoV-2 infection, no benefit was observed with interferon alfa-2b and Kaletra plus interferon alfa-2b treatment beyond standard care. Further trials in appropriately randomized design may contribute to validate the effective role and safety profile of the test drugs.

Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), posed an enormous threat to public health¹⁻⁴. Since the first case with SARS-CoV-2 was published in December 2019, the laboratory-confirmed cases are continuously escalating day to day and spread like wildfire to more than 200 countries and territories^{5, 6}. COVID-19 cases are frequently associated with respiratory and multiorgan dysfunction that result in deaths⁷⁻⁹. Accordingly, the use of antiviral drugs in patients with this disease have triggered questions and whether currently antiviral drugs could be effectively cured this disease prompts a critical consideration.

Based on results from previous research, the protease inhibitor Kaletra, in combination with interferon, have modest activity against SARS-CoV and Middle East respiratory syndrome (MERS)-CoV¹⁰⁻¹². However, A recent research from Cao and colleagues suggested Kaletra alone had a limited role in COVID-19 treatment¹³. Considering that coronaviruses can hijack the antiviral responses of type I interferon through structural and non-structural proteins, utilizing interferon could provide an effective treatment to target and eliminate SARS-CoV-2^{14, 15}. However, Channappavanar et al have demonstrated that the delayed interferon-I expression was detrimental in the context of SARS-CoV-1 infection in mice¹⁶. In addition, retrospective studies with interferon combined with ribavirin have not shown an obvious benefit in patients with MERS^{12, 17}.

Together, it is imperative to acknowledge that the therapeutic potential of Kaletra and interferon is still controversial in treatment for COVID-19 and begs for further investigation.

The purpose of this study was to evaluate the efficacy and safety of interferon alfa-2b and Kaletra plus interferon alfa-2b for SARS-CoV-2 infection in adult patients hospitalized with COVID-19.

Methods

Study design and participants

This retrospective cohort study was conducted on confirmed SARS-CoV-2 infected patients who were admitted to Beijing Ditan Hospital from Jan.13 2020 to Apr. 23. The institutional review boards approved this study and patient-level informed consent was waived owing to its retrospective nature. SARS-CoV-2 infection was diagnosed by RT-PCR assay of respiratory tract samples tested by the local Center for Disease Control or by our institutional laboratory. Pneumonia was defined as new, lower respiratory tract symptoms such as fever or chills, cough or shortness of breath, and new focal chest signs, coinciding with new onset or progressive pulmonary infiltrates on chest radiography. The severity of COVID-19 was defined in accordance with the China's COVID-19 management guidelines (version 7.0).

All confirmed patients were offered treatment with standard care including as necessary, supplemental oxygen, antibiotic agents, or traditional Chinese medicine. The potential antiviral therapy for SARS-CoV-2 assigned two groups: receiving Kaletra (500 mg twice daily, orally) plus interferon alfa-2b (interferon, 5 million units twice daily, nebulization) or interferon alfa-2b alone. Initially, a total of 196 cases were identified (Figure 1.). Among these, cases (n=29) were excluded for patients who were younger than 18 years and critically ill patients. Among the 167 remaining participants, cases were excluded (n=44) on the basis of other antiviral therapy including oseltamivir, chloroquine phosphate, and ribavirin. Eventually, 123 participants were enrolled in the study. The main exposure divided into two groups: Kaletra plus interferon alfa-2b therapy (n=67), defined as the use of Kaletra and interferon alfa-2b combination, and interferon alfa-2b alone (n=44). The comparator group was treatment with standard care without use of Kaletra and interferon alfa-2b (n=12). The final groups for the 123 included cases were: standard care group (n=12), interferon alfa-2b group (n=44), Kaletra plus interferon alfa-2b group (n=67).

Data collection

Data on patients' demographics, underlying comorbidities, clinical presentation, oxygen-support requirements and laboratory results were recorded. The time to SARS-CoV-2 RNA clearance in respiratory specimens of patients with confirmed diagnosis were also assessed. Virus clearance was defined as the time from admission until the RT-PCR assay was negative on 2 occasions. To assess Kaletra and interferon alfa-2b safety profile, the occurrence of nausea, diarrhea, rash and serial levels of white blood cell (WBC) count, neutrophil count, hemoglobin, platelet count, aminotransferase, bilirubin, and creatinine kinase were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0..

Outcomes

The primary endpoint for this study was the duration of oxygen-support requirement and virus clearance time.

Statistical analysis

All analyses were conducted with IBM SPSS Statistics, version 19.0 (SPSS Institute, Chicago IL, USA). Categorical variables were conducted by the chi-square (χ^2) and Fisher's exact tests. Normally distributed variables were compared using the Student's t-test, whereas non-normally distributed variables were conducted by the Kruskal-Wallis test. Two-sided P values of 0.05 were considered statistically significant. The time to oxygen-support requirement, virus clearance were portrayed by Kaplan-Meier plot. Associations between therapies and these outcomes were assessed by Cox proportional hazards regression.

Results

Baseline Characteristics of the Patients

The baseline demographic and clinical characteristics of the 123 patients with SARS-CoV-2 were shown in Table 1. A total of 62 patients (50.41%) were men, the age range was 18 to 92 years, and the median age was 41 years (interquartile range, 32 to 57). The number of comorbidities was 55 (44.72%), and hypertension accounted for the majority. At baseline, the majority of patients were mild patients (105 [85.37%]), while severe patients (18 [14.63%]) were relatively less. 82.93% of the patients were observed fever on presentation, while the median body temperature on admission was 37.0 (interquartile range, 36.5 to 37.6). A total of 54 patients (43.90%) enrolled requiring oxygen-support, while low flow oxygen requirements accounted for majority (39.84%). In terms of laboratory results, blood indices of CoV-19 patients were within the normal range on the admission, including peripheral white cell count, platelets, C-reactive protein, serum creatinine, aspartate transaminase, alanine transaminase, bilirubin, LDH, and creatine kinase. Patients in the 3 groups were similar in age, sex, comorbidities, and baseline laboratory results at enrollment ($p < 0.05$).

Outcomes

Crude analysis showed that the duration of oxygen-support requirement in therapy groups had no significant differences compared to standard care group (median, 13 days [interquartile range:8, 16], 11 days [interquartile range:7, 22] vs 13 days [interquartile range:7, 24]; $P = 0.98$; Table 3). Meanwhile, there was no difference in virus clearance time among 3 groups. Using Cox proportional hazards regression adjusting for baseline covariate, there was no significant association of Kaletra /interferon alfa-2b with faster SARS-CoV-2 RNA clearance (HR, 0.85 [95% CI, 0.45–1.61]; $P = 0.61$ in interferon alfa-2b group vs HR, 0.59 [95% CI, 0.32–1.11]; $P = 0.10$ in Kaletra plus interferon alfa-2b group, Table 4, Figure 2). The duration of oxygen-support requirement in therapy groups similarly showed no significant association (HR, 1.46 [95% CI, 0.57–3.75]; $P = 0.43$ in interferon alfa-2b group vs HR, 1.06 [95% CI, 0.43–2.63]; $P = 0.90$ in Kaletra plus interferon alfa-2b group, Table 4, Figure 3).

Safety Endpoints

Kaletra and interferon alfa-2b therapy was well tolerated by the exposed group without premature discontinuation secondary to adverse effects. There were no significant differences among the 3 group in the incidence of nausea, diarrhea, rash, leukopenia, neutropenia, anemia, thrombocytopenia, increased creatinine, and et al (Table 2). However, the incidence of increased creatine kinase over the therapy course was higher in the exposed group (15.91% in interferon alfa-2b group vs 20.90% in Kaletra/ interferon alfa-2b group) than in the standard care group (0), despite without statistical difference. Aside from anemia and increased bilirubin, the occurrence of adverse effects were lower in standard care group than in therapy groups.

Discussion

Effective interventions for treating patients with SARS-CoV-2 infection are still urgently needed. While benefit of Kaletra and interferon alpha-2b was suggested by preclinical studies, the present study showed that neither interferon alfa-2b nor Kaletra plus interferon alfa-2b added to standard care were not associated with the duration of oxygen-support requirement and virus clearance time compared with standard care alone. The question of whether interferon alfa-2b or Kaletra plus interferon alpha-2b treatment could have clinical benefit in COVID-19 is an critical crucial one that requires further study.

Prior research from Y. Arabi et al showed that Kaletra/interferon therapy were not associated with clinical improvement or CoV RNA clearance, which are consistent with our study^{13, 17, 18}. Besides, the Society of Critical Care Medicine provides recommendation against of use Kaletra in critically ill COVID-19 patients¹⁹. However, previous studies also showed Kaletra and interferon alfa-2b have benefits in clinical improvement for patients with SARS-CoV and MERS-CoV infection^{10-12, 20}. The reasons for the similar treatment with different results of clinical outcome and viral RNA clearance are uncertain. The nonrandomized design, differences of baseline characteristics, and small sample sizes might be the related to the inconsistency.

Additionally, owing to the nonstandard initiation of therapy, such research are prone to two biases: indication bias and immortal time bias.

To assess safety profile of interferon alfa-2b and Kaletra plus interferon alfa-2b, the incidence of nausea, diarrhea, rash and levels of WBC count, neutrophil count, hemoglobin, platelet count, alanine aminotransferase, bilirubin, and creatinine kinase were compared and no differences were observed among the 3 groups over the hospitalization stay. Of note, we found that the incidence of increased creatine kinase were higher in patients treated with interferon alfa-2b or Kaletra plus interferon alfa-2b than in standard care group. This change may be related to interferon alpha-2b therapy, which is in accordance with the previous reports^{21, 22}. Otherwise, recent research from Yanchao Pan et al consider that the increased creatine kinase is correlate with virus²³. Further studies might confirm or exclude the cause of creatinine kinase through in vitro or animal trails.

The retrospective, non-randomized nature is the limitations of this study. Inevitably, selection and unmeasured confounding bias couldn't be excluded completely. Further interventions should be evaluated ideally in randomized, controlled clinical trials. Otherwise, such methods are generally accepted to not always be practical in the emerging context. The small number of control group is another limitation of this study. Thus, further research should enlarge the sample size to make the results more accurate.

In patients with confirmed SARS-CoV-2 infection, no benefit was observed with interferon alfa-2b and Kaletra plus interferon alfa-2b treatment beyond standard care. Further trials in appropriately randomized design may contribute to validate the effective role and safety profile of the test drugs.

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Table legends

Table 1. Baseline characteristics of 123 patients with SARS-Cov-2 infection.

Table 2. Summary of adverse events in the safety population.

Table 3. The difference of therapy group and standard group in the duration of oxygen-support and CoV RNA clearance time.

Table 4. Association of Kaletra/Interferon with the duration of oxygen-support and CoV RNA clearance in Patients With SARS-CoV-2 infection.

Figure legends

Fig. 1 Flowchart demonstrates study population and exclusion criteria.

Fig. 2 Cumulative incidence of the duration of oxygen-support requirement from baseline.

Fig. 3 Cumulative incidence of the virus clearance time from baseline.

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Table.docx available at <https://authorea.com/users/340256/articles/467349-comparative-therapeutic-efficacy-of-interferon-and-combination-kaletra-plus-interferon-alpha-2b-against-sars-cov-2>



