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Case Report

Treatment of severe pneumonia due to COVID-19 with peginterferon alfa 2a

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ABSTRACT

The outbreak of the new coronavirus disease 2019 (COVID-19) has spread rapidly worldwide. Until now, no definite effective treatment has been identified. We reported 3 patients with severe COVID-19 treated with pegylated interferon alfa 2a with satisfactory recovery. Based on these observations, randomized studies with interferons should be considered in deteriorating patients infected with COVID-19.

Introduction

The outbreak of pneumonia due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originating in Wuhan, China has rapidly spread to become a pandemic as assessed by the World Health Organization. As of April 19, 2020, the total number of confirmed cases has reached 2,241,359 cases, with a total of 152,552 deaths worldwide [1]. There is an urgent need to develop an effective regimen for COVID-19, given the high infectivity of this novel virus and the rapid progression of this disease.

The majority of patients with SARS-CoV-2 seem to have a non-complicated course, with an asymptomatic or mild presentation. However, the disease may progress rapidly to severe pneumonia and acute respiratory distress syndrome (ARDS), requiring mechanical ventilation in a considerable number of patients [2]. Patients with a severe presentation of COVID-19 often present with lymphopenia, leukopenia and elevated inflammatory markers, demonstrating a significant immune response [2,3].

There is some evidence that severe deterioration, leading to ARDS is driven by a cytokine storm and that early intervention and suppression of this cytokine dysregulation may play a role in preventing the severe stages of the disease [4]. Here we report on 3 patients with COVID-19 who received peginterferon alfa 2a at the time they developed respiratory distress, with satisfactory clinical and radiographic recovery.

Case presentations

Patient 1

On March 1, 2020 a 38-year-old male who was otherwise healthy was admitted to our institution with a history of high-risk exposure to SARS-CoV-2. He had no symptoms of COVID-19 and was doing well. He arrived in the United Arab Emirates from Italy on February 21. He denied any fever, rhinorrhea, nasal congestion, cough, sore throat, shortness of breath, or malaise. Oropharyngeal and nasopharyngeal swabs were positive for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) assay. On admission he was found to have a fever of 38.9 °C, with a blood pressure 142/94 mm/Hg, pulse 78 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation 98 % when breathing ambient air. Both lungs were clear on auscultation and the remainder of the physical examination was unremarkable. Laboratory results revealed thrombocytopenia, with a lymphocyte count of 0.90 (1.50–4.00) cells/μL. His inflammatory markers were elevated, with C-reactive protein (CRP) of 28.1 (0–5) mg/L. Liver function and renal function were within the normal range. The respiratory virus panel (BioFire, FilmArray, bioMérieux, Salt Lake City, UT) was negative for influenza A and B as well as Middle East

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Respiratory Syndrome (MERS CoV). A chest X-ray done on admission revealed infrahilar infiltrates.

The patient was diagnosed with COVID-19. Supportive care and therapy were initiated with darunavir 600 mg orally twice daily, ritonavir 100 mg orally twice daily, and hydroxychloroquine 400 mg orally once daily, with close monitoring of his clinical status. His QTc interval at baseline and on follow-up were normal. On March 6 (hospital day 6), his chest X-ray showed worsening infiltrates and he had persistent fever and worsening lymphopenia. Favipiravir was added to his regimen at a loading dose of 1600 mg orally every 12 h, followed by 600 mg orally every 8 h, and hydroxychloroquine was discontinued. He continued to have daily fever (maximum temperature 39.8 °C), and on March 9 he developed a dry cough and his oxygen saturation decreased to 90 % when breathing ambient air. His CRP increased to 84.3 mg/L. A computed tomography (CT) scan on March 9 showed diffuse bilateral confluent and patchy ground glass and consolidative pulmonary opacities in both lungs, predominantly in right upper

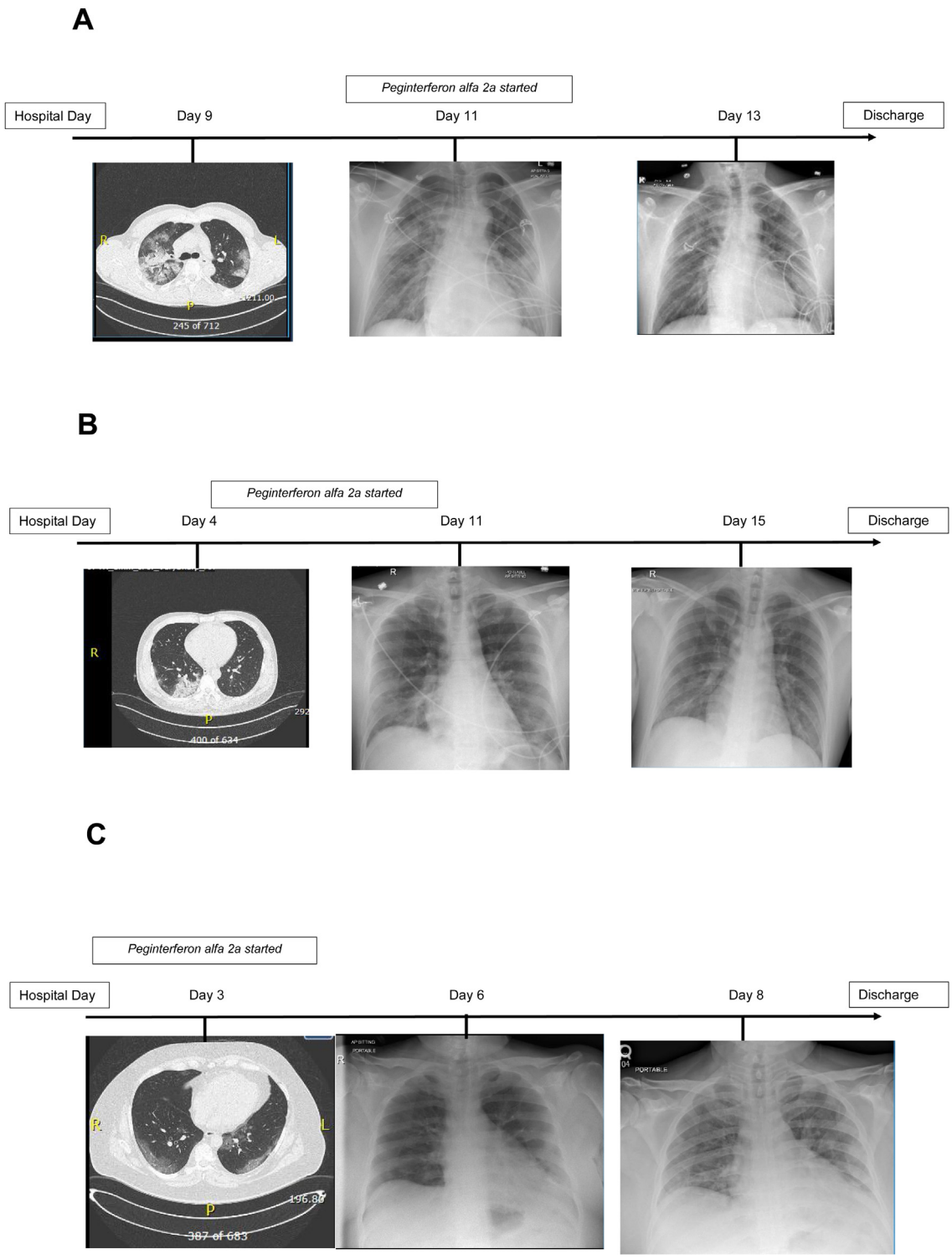

Fig. 1. Chest computed tomography scan and x-rays of patient 1 (A), patient 2 (B), and patient 3 (C) before and after peginterferon alfa 2a.

and left lower lobes. A sputum culture with gram stain as well as methicillin-resistant *S. aureus* nasal swab were collected, and an empiric antibacterial regimen of cefepime and intravenous vancomycin was initiated to cover a possible hospital-acquired pneumonia.

The diagnosis was modified to COVID-19, severe pneumonia. The patient continued to have persistent fever and peginterferon alfa 2a was started on March 11 (hospital day 11) at 180 μg for 1 dose administered subcutaneously. Cefepime and vancomycin were de-escalated to amoxicillin-clavulanate when sputum culture showed growth of normal oral flora and the MRSA nasal swab was negative. The next day after peginterferon administration, the patient became afebrile. No adverse event was reported. The supplemental oxygen was discontinued, and his oxygen saturation level returned to 96–97% on March 14 (hospital day 14) when breathing ambient air. Test results on the following day showed recovered lymphocyte count to 1.06 cells/μL. CRP returned to normal range. A repeat chest X-ray showed partial resolution of previous lesions (Fig. 1A). Two consecutive oropharyngeal swabs on March 12 and March 13 were both negative for SARS-CoV-2 and a sputum sample was also negative on March 14 for SARS-CoV-2. Over the next few days, his clinical status gradually improved. The patient was discharged on March 18 (hospital day 18).

Patient 2

A 37-year-old male presented with fever and dry cough and was admitted to our institution on March 19, 2020. The patient was known to have been exposed to a SARS-CoV-2 positive patient and oropharyngeal and nasopharyngeal swabs were positive for SARS-CoV-2. The patient had no significant past medical history and reported no other symptoms.

Physical examination showed a body temperature of 39.2 °C, blood pressure 135/64 mmHg, pulse 102 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation was 100 % when breathing ambient air. Laboratory results on admission showed a complete blood count that was within normal limits and mildly elevated CRP 15 mg/L (Table 1). A chest X-ray on admission was unremarkable. He received therapy for COVID-19 with hydroxychloroquine 400 mg orally once daily and lopinavir/ritonavir 400 mg/100 mg orally twice daily for 10 days. The patient continued to have fever; therefore, sputum culture and gram stain were obtained and the patient was initiated on empirical antibacterial therapy with azithromycin.

A CT scan done on March 22 (hospital day 4) showed bilateral patchy ground glass infiltrates in the upper lobes and lower lobes (Fig. 1B). A larger area of infiltrate was present in the right lower lobe in the posterobasal segment, which had an air bronchogram in it. He continued to have persistent fever, along with elevated ferritin levels of 908 μg/L and favipiravir was added to his regimen at a loading dose of 1600 mg orally every 12 h followed by 600 mg orally every 8 h. On March 25 (hospital day 7) the patient's clinical condition worsened, with his oxygen saturation decreasing to 93 % when breathing ambient air and he was initiated on oxygen at 2 L/min. His CRP increased to 55 mg/L and ferritin continued to increase to 1847 μg/L (Table 1). His lymphocyte count decreased to 0.56 cells/μL. Peginterferon alfa 2a was initiated on that day at 180 μg per week for two doses administered subcutaneously. He became afebrile the next day after administration of the first dose of peginterferon. He was also started empirically on cefepime for possible hospital-acquired pneumonia, which was later de-escalated to amoxicillin-clavulanate when sputum cultures showed growth of normal oral flora. Over the course of the next few days, his oxygen requirements decreased and was able to maintain an oxygen saturation of 98–100% when breathing ambient air. His lymphocyte count continued to increase and inflammatory markers were improving and on April 3 (hospital day 16), his lymphocyte count increased to 1.48 cells/μL and his CRP normalized at 4.5 mg/L. A chest X-ray showed interval improvement, without complete resolution of bilateral lower lung airspace disease. The patient continued to improve and was discharged from the hospital on April 9 (hospital day 22).

Patient 3

A 61-year-old year old male with a known past medical history of type 2 diabetes mellitus, hypertension and hyperlipidemia was admitted to our institution on March 23, 2020 with a positive

Table 1
Laboratory Tests of the 3 Patients Before and After Administration of Peginterferon alfa 2a.

	Reference Range	Patient 1[a]				Patient 2[b]				Patient 3[c]			
Date	–	1/3/20	11/3/20	12/3/20	14/3/20	19/3/20	25/3/20	26/3/20	3/4/20	23/3/20	25/3/20	26/3/20	31/3/20
Hospital Day	–	1	11	12	14	1	7	8	16	1	3	4	9
ALP, IU/L	40 – 129	–	35[d]	–	–	77	55	52	77	—	47	46	43
ALT, U/L	17 – 63	–	20	–	–	58	28	31	90[e]	—	35	34	40
AST, U/L	< 40	–	25	–	–	42[e]	37	40	43[e]	—	48[e]	45[e]	34
CRE, μmol/L	59 – 104	91	79	78	62	113[e]	80	83	65	—	49[d]	59	60
Hb, g/L	132 – 173	162	163	157	143	142	141	139	134	—	126[d]	125[d]	109[d]
HCT, L/L	0.39 – 0.49	–	–	–	–	0.42	0.4	0.4	0.4	—	0.37[d]	0.38[d]	0.33[d]
CRP, mg/L	< 5	7.6[e]	84.3[e]	92[e]	31.2[e]	15[e]	55[e]	82.4[e]	4.5[e]	—	39.3[e]	96.8[e]	66.4[e]
LDH, U/L	135 – 225	–	–	–	–	–	–	–	–	333[e]	—	—	318[e]
LYM, cells/μL	1.5 – 4	0.9[d]	0.8[d]	0.8[d]	0.8[d]	0.92[d]	0.56[d]	1.01[d]	1.49[d]	—	1.43[d]	1.37[d]	1.19[d]
NEUT, 10^9/L	1.8 – 7.7	4.7	6.9	7	2.2	4.34	3.9	5.13	1.43	—	3.68	3.94	4.39
PLT, 10^9/L	140 – 400	180	267	304	357	268	228	250	483[e]	—	153	172	615[e]
RBC, 10^{12}/L	4.3 – 5.7	5.2	5.3	5.1	4.7	4.8	4.84	4.8	4.7	—	4.04	4.06	3.57[d]
SF, μg/L	36 – 480	–	–	–	–	579[e]	1847[e]	—	1581[e]	1267[e]	—	—	989[e]
TBIL, μmol/L	5 – 21	–	9.9	–	–	11.9	10.5	16.6	6.1	—	18.3	18.8	10
WBC, 10^9/L	4.5 – 11	6.2	8	8.1	3.5	5.56	4.76	6.63	3.96[d]	—	5.72	6.12	6.46

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRE, creatinine; Hb, hemoglobin; HCT, hematocrit CRP, C-reactive protein; LDH, lactate dehydrogenase; LYM, absolute lymphocyte count; NEUT, absolute neutrophil count; PLT, platelet count; RBC, red blood cell count; SF, serum ferritin; TBIL, total bilirubin; WBC, white blood cell count.

[a] Peginterferon alfa 2a was initiated on hospital day 11.
[b] Peginterferon alfa 2a was initiated on hospital day 7.
[c] Peginterferon alfa 2a was initiated on hospital day 3.
[d] the value in the patient was below normal.
[e] the value in the patient was above normal.

nasopharyngeal and oropharyngeal swab for SARS-CoV-2. The patient had returned from a trip to New York city one week earlier. He reported fever, malaise, myalgias and diarrhea. On admission, he was febrile (38.1 °C), blood pressure 136/63 mmHg, pulse 92 beats per minute, respiratory rate 17 breaths per minute, and oxygen saturation 96 % when breathing ambient air. His lungs were clear on auscultation. Laboratory studies revealed a slightly elevated CRP of 20 mg/L and elevated ferritin of 1267 μg/L (Table 1). All other laboratory tests were within normal limits. The respiratory viral panel was negative for influenza A and B and MERS-CoV. A chest X-ray was done on admission and revealed clear lungs, with no apparent infiltrates. The patient was started on lopinavir/ritonavir 400/100 mg orally twice daily and favipiravir at a loading dose of 1600 mg orally every 12 h followed by 600 mg orally every 8 h, for COVID-19, and were continued for 10 days.

On March 25 (hospital day 3) the patient's oxygen saturation decreased to 93 % and he was started on oxygen 2 L/min. A CT scan of the chest was done and showed bilateral ground glass opacities, with distribution more noted in the lower lobes (Fig. 1C). This was accompanied by an increase in the CRP to 39.3 mg/L. Based on the deterioration of the patient's state he was started on peginterferon alfa 2a 180 μg per week for 2 doses administered subcutaneously.

His fever subsided the day after initiating peginterferon alfa 2a. His condition improved over the next few days, and his oxygen saturation returned to 98 % on March 31 (hospital day 9). Negative PCR testing for SARS-CoV-2 was confirmed on March 28 and March 29. The sputum sample was also negative for SARS-CoV-2 on March 30. The chest X-ray showed unchanged infiltrates on March 28 (hospital day 6). (Fig. 1C). Inflammatory markers continued to decrease, including CRP level of 33.9 mg/L and ferritin 927 μg/L. He was discharged on April 2, 2020 (hospital day 11).

Discussion

Although there has been a plethora of publications on the clinical presentation and management of COVID-19 over the past three months, our understanding of the pathophysiological changes in this infection remains limited. To date, there is no definite treatment identified which makes management of this disease challenging. Here we present a case series of three patients with severe COVID-19 pneumonia who were treated with pegylated interferon alfa 2a. The patients had virological clearance within a few days of treatment and improvement of the clinical condition as reflected by the decrease in oxygen requirements, normalization of reactive parameters and improvement of radiological abnormalities. None of the mentioned patients progressed to require mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

Patients with COVID-19 as reported by Huang et al., typically present with mild symptoms including fever, myalgia or fatigue, and dry cough, with the majority having a favorable outcome [3]. A subset of patients may progress within a week of the onset of their symptoms to have dyspnea and hypoxemia, which may rapidly progress to ARDS, or end-organ failure [3]. The 3 patients described here had features that suggested clinical deterioration and possible clinical progression to ARDS, including high fever, elevated inflammatory markers, and elevated coagulation markers [5]. Additionally, CT findings in our patients closely resembled those reported in the literature whereby involvement was bilateral, with lesions evident in the lower lobes and combination of ground-glass opacities together with consolidation, which is observed as the disease progresses [6].

It has been suggested that COVID-19 presents in three stages: (1) an initial asymptomatic incubation period and a non-severe symptomatic phase; (2) a severe respiratory symptomatic phase (marked by high viral loads) in a small subset of patients; and (3) a later phase of the disease marked by cytokine storm and severe lung inflammation [7]. Given that our patients presented with features showing progression into the later phases of the disease it was prudent to initiate therapy to enhance the immune response at this critical juncture to prevent clinical deterioration into the fatal phase of the disease.

Immunomodulatory therapy including interferons have been investigated in the management of coronavirus infections including MERS-CoV and SARS [8]. Type 1 interferon (IFN-1) is among the first cytokines produced during a viral infection and is involved in inflammation, signaling and immunomodulation [9]. It interferes with viral replication and plays a major role in antiviral immunity [9]. Interferons have been extensively studied for their activity against coronavirus in cell culture, animal models, and clinical studies [9]. While the Type I interferons (alpha and beta) are the most studied, there have been several studies of the Type II (gamma) and III (lambda) interferons [10,11]. Interferon beta was found to be the most potent interferon subtype in various in vitro studies conducted in SARS-CoV and MERS-CoV [10,12,13].

Interferon alfa was investigated in one single arm study with corticosteroids and one open-label randomized controlled trial with corticosteroids, showing variable outcomes in SARS-CoV [14,15]. Both interferon alfa and interferon beta with ribavirin were studied in MERS-CoV in observational studies [16–18]. Two of the studies revealed no difference in treatment outcomes, and a third trial showed a reduction in mortality with the use of interferon beta. However, the observational nature of these trials makes it difficult to draw conclusions on the true efficacy of therapy with interferon [16–18].

Most recently a pre-print was published on a retrospective study investigating interferon alfa-2b in SARS-CoV-2 in its nebulized form in 77 patients. The trial compared the outcomes of patients who received nebulized interferon alfa-2b or umifenovir monotherapy, versus combination of interferon alfa-2b with umifenovir. The study investigators showed that patients who received interferon therapy experienced more rapid viral clearance compared to those treated with umifenovir alone. The retrospective design of this study in addition to an imbalance in patient demographics at baseline (patients on umifenovir monotherapy were older, had more co-morbidities and presented for admission later in course of their disease) makes it difficult to extrapolate data to a broader patient population. Despite these limitations, this study presents some evidence of the role of interferon in the management of COVID-19 that could be corroborated in future clinical trials [19].

The most recent edition of the Chinese guidelines for management of COVID-19 continue to recommend interferon alfa by nebulization [20]. Although the nebulized formulation would theoretically be more tolerated by minimizing systemic side effects and ensuring adequate concentrations in the respiratory tract, we did not observe any side effects in our patients with the subcutaneous administration. This could be due to the fact that they only only received 1 or 2 doses, which may not have been sufficient to elicit the toxic side effects usually observed with prolonged pegylated interferon alfa 2a therapy (including hepatoxicity, bone marrow suppression and neuropsychiatric side effects).

Our report has a few limitations. First, this is a small case series that included no controls. This makes it unclear to conclude if the patients would have improved without the use of pegylated interferon. Second, all patients were treated with multiple other agents (including antiretrovirals, favipiravir and hydroxychloroquine), and it is not possible to determine whether the improvement observed could have been related to other therapies or attributed solely to the pegylated interferon. Third, the timing of administration of this medication was not standardized along the

course of illness, making it difficult to ascertain the same outcomes in other patients if used.

Additional clinical trials will enhance our understanding of the role of interferon in COVID-19 management and there are several ongoing registered clinical trials investigating the role of interferon alfa and interferon beta in COVID-19 alone and in combination with various agents, including lopinavir/ritonavir, hydroxychloroquine, and/or ribavirin [21].

Conclusion

In this preliminary uncontrolled case series of 3 severely ill patients with COVID-19, administration of pegylated interferon was followed by clear improvement in the patients' clinical status within 24−36 h of administration of the drug. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in a controlled clinical trial.

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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