Case Report

Efficacy of anti-inflammatory drug ulinastatin in coronavirus disease 2019: A case report

Rupa Chatterjee[1], ShahafazIbi Meethal Puthiya Purayil[1], Raneesh Kumar Ramakrishnan[2], Rajesh Sankaran[2], Changam Sheela Sasikumar[3]

From [1]Junior Medical Resident, [2]Director and Intensivist, Department of Covid Ward, Hycare Superspeciality Hospital, [3]Head, Department of Clinical Research, Hycare Superspeciality Hospital, Chennai, Tamil Nadu, India

ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory coronavirus 2, can affect the respiratory system as well as other systems of the body. It has now become a pandemic and poses a global health emergency. We report the case of a COVID-19-positive 50-year-old male patient with multiple, ground-glass opacities in bilateral lungs. The disease did not respond well to tocilizumab administration and the condition of the patient gradually worsened. We administered ulinastatin along with high doses of steroids. We observed that the overall performance of a combination of ulinastatin and high-dose steroids proved to be effective and routine use of ulinastatin is a potent method of treatment in COVID-19 patients developing acute respiratory distress syndrome, which may save other patients with a similar background.

Key words: Anti-inflammatory, Coronavirus disease 2019, Ulinastatin

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), can affect the respiratory system as well as other systems of the body [1]. It has now become a pandemic and poses a global health emergency [2]. While the majority of patients with COVID-19 have mild-to-moderate symptoms, approximately 14% of the patients may progress to severe pneumonia and exhibit considerable fatality [3]. To date, there are no specific therapeutic agents or vaccines available. Immunologic characteristics of patients with severe COVID-19 exhibit remarkably elevated serum levels of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β, characterized as a cytokine storm. The cytokine storm is believed to play a critical role in COVID-19 progression, deterioration, and even death [3]. Strategies to dampen the inflammatory responses are, therefore, proposed.

Ulinastatin is a glycoprotein extracted from the fresh human urine. It inhibits the activity of various proteolytic enzymes and has been widely used for the treatment of acute pancreatitis (AP). Meanwhile, ulinastatin has been demonstrated as an important anti-inflammatory and antioxidation agent and has been clinically used as a potential treatment for circulatory shock, severe sepsis, and acute respiratory distress syndrome (ARDS) [4-6]. Assuming the same pathophysiology to be functional in the ARDS of COVID-19 pneumonia, ulinastatin could limit the inflammation of the alveolar membrane and the systemic inflammatory response, thereby having a major role in the recovery of patients with severe and critical respiratory symptoms. We report the case of a COVID-19-positive 50-year-old male patient who was successfully treated with a combination of ulinastatin and high-dose steroids.

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CASE REPORT

A 50-year-old obese male with no known comorbidities was admitted to a hospital of South India with complaints of fever, cough, and shortness of breath for 5 days. The patient was tested COVID positive with computed tomography (CT). COVID reverse transcription polymerase chain reaction (RT-PCR) done outside revealed a negative result but CT showed CO-RADS-5 with multiple ground-glass opacities in bilateral lungs involving all lobes. The medical history and family history of the patient were non-significant.

On examination, he recorded a temperature of 101 degrees Fahrenheit, blood pressure of 110/80 mmHg, pulse rate of 100/min, respiratory rate of 52 (tachypnea), and oxygen saturation in room air

Correspondence to: Dr. Rupa Chatterjee, Hycare Superspeciality Hospital, No 37&38 Razack Garden Road MMDA Colony, Arumbakkam, Chennai - 600 106, Tamil Nadu, India. E-mail: chatterjee.rupa@gmail.com

was 72% which increased up to 86% with 15 l of oxygen through non-rebreather face mask (NRBM). Respiratory system examination revealed decreased air entry in the bilateral lungs with crept.

According to the Indian guidelines [7] and based on the severity of the disease, the patient was initiated on inj. methylprednisolone 80 mg Q8h, inj. remdesivir 100 mg OD after a loading dose of 200 mg on day 1, inj. low-molecular-weight heparin 0.6 mg Q12h along with inj. tocilizumab 200 mg Q12h (2 doses), inj. piperacillin + tazobactam 4.5 g Q6h, inj. doxycycline 100 mg Q12h, T. azithromycin 500 mg OD, T. Vitamin C 500 mg OD, and T. zinc 20 mg Q12h.

Investigations show the following values: IL-6=39.36, ferritin=557.00 μg/L, and D-dimer=0.50 mcg/mL. On the following day, in view of his persistent tachypnea, he was commenced on intermittent bilevel positive airway pressure (I/E=18/12) with intermittent 15 L of oxygen through NRBM. On serial chest X-ray (CXR) monitoring, there was a worsening of bilateral heterogeneous opacities on the right side but the clinical condition of the patient remained the same with no fever spikes, respiratory rate maintaining at 38–40, and saturation maintaining at 88% with oxygen support (Fig. 1a). After 2 days, COVID RT-PCR was repeated which revealed a positive result. On the 5th day of admission to the hospital, a CXR was done (Fig. 1b) and investigations revealed values of IL-6=526.8, ferritin=544.10 μg/L, and D-dimer=2.26 mcg/mL.

Medications were revised and inj. ulinastatin, 200,000 units in 100 ml NS i.v Q8h, was added and inj. remdesivir was withheld. The condition of the patient improved in terms of respiratory rate (26–28/min) with a reduction in the oxygen dependency (4–6 L through NRBM) to maintain a saturation above 95%. On the 9th day, serial CXR monitoring was done which revealed resolution of the pneumonitic patches to an extent with reemergence of air pockets (Fig. 2a).

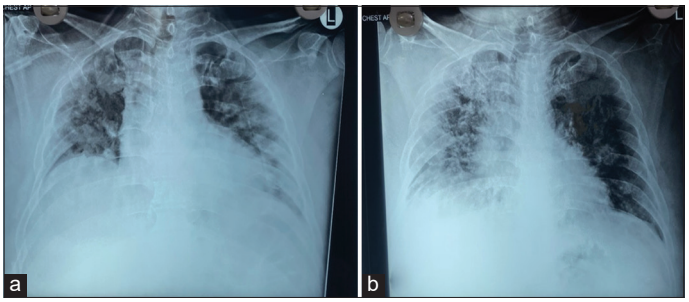

Figure 1: Chest X-ray done on (a) day 1 and (b) day 6

After 10 days, the CXR was performed again (Fig. 2b) and the investigations such as IL6=85.92, ferritin=197.50 mg/l, and D-dimer 0.12 mcg/mL were done. Henceforth, the frequency of administration inj. ulinastatin was gradually reduced from 200,000 units Q8h and was withheld after a total of 9 days of administration. After 2 weeks, the CXR was done (Fig. 2c) and the patient was counseled for deep breathing and other respiratory exercises. After 20 days of admission, the patient was discharged maintaining a respiratory rate of 22/min and saturation of 90% at room air. Post-discharge instructions were given to the patient.

DISCUSSION

The cytokine storm is believed to play an essential role in the pathogenesis of COVID-19 and might be correlated with disease severity and fatality. It is thought to be the reason for rapid multiorgan failure [8]. The study of SARS-CoV showed that virus-infected lung epithelial cells produced IL-8 in addition to IL-6. IL-8 is a well-known chemoattractant for neutrophils and T cells. Infiltration of a large number of inflammatory cells was observed in the lungs from severe COVID-19 patients and these cells presumably consist of a constellation of innate immune cells and adaptive immune cells. Therefore, modulation of the immune response or suppression of over-reactive cytokine production may prove crucial in severe cases [9].

Ulinastatin, an intrinsic broad-spectrum protease inhibitor, could effectively inhibit a variety of cell proteolytic enzymes and have multifunctional therapeutic mechanisms. First, ulinastatin has an inhibitory effect on the production of inflammatory cytokines and adhesion molecules [10]. Meanwhile, ulinastatin improves the stability of the lysosomal membrane and reduces the synthesis and delivery of lysosomal enzymes, thus scavenging oxygen or hydroxyl radicals. Treatment with ulinastatin reduces the level of TNF-α and IL-1β in a dose-dependent way. TGF-β1 and IL-10 are T-cell-related cytokines characterized as immunosuppressive or anti-inflammatory mediators. The previous studies have shown that ulinastatin can inhibit the expression of TNF-α and IL-1β, and increase the levels of IL-2 and IL-10 [11,12]. The studies on the mechanism of the anti-inflammatory effect of ulinastatin have mainly been focused on the roles of these cytokines. A recent meta-analysis of 33 randomized controlled trials involving 2344 patients of ARDS showed that as compared to conventional therapy, ulinastatin was

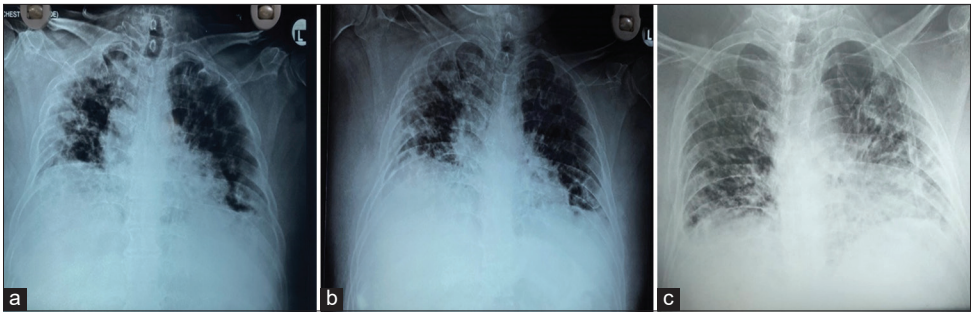

Figure 2: Chest X-ray done on (a) day 9; (b) day 11; (c) day 14

superior in reducing mortality, ventilator-associated pneumonia, duration of mechanical ventilation, length of hospital stay, and increasing the patients oxygenation index. The meta-analysis had also demonstrated a significant reduction in levels of TNF-α, IL-1β, IL-6, and IL-8 [6]. A consensus document from China has recommended high-dose ulinastatin in the prevention and management of cytokine storm in patients with COVID-19 [13].

In recent years, evidence has accumulated that immune reactions and immune cells such as CD4+ T cells and Tregs play important roles in the AP pathogenesis [14,15]. Hence, inhibiting pro-inflammatory mediators [16,17] and regulating immune reactions are important considerations in the therapy of severe AP [15]. It has been confirmed that ulinastatin can regulate the immunological function through these special immune cells [18,19]. The pro-inflammatory cytokines such as IL-1β, IL-10, and TNF-α have been shown to play an important role in the pathogenesis of AP causing tissue damage and organ dysfunction. In the course of AP, multiorgan damage caused in the early stage associated with systemic inflammatory response, followed by pancreatic necrosis in the late stage are the two most important events responsible for mortality [20]. The intervention in the early stage by targeting an inflammatory response may be an effective treatment strategy in the treatment of AP [21].

CONCLUSION

A high dose of ulinastatin treatment is safe and potentially beneficial for the patients with COVID-19, with rapid improvement of clinical symptoms, blood parameters, and absorption of the pulmonary lesions.

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