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ANTI-INFLAMMATORY DRUG ULINASTATIN MIGHT REDUCE MORTALITY IN MECHANICALLY VENTILATED COVID-19 PATIENTS

Medicine

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ABSTRACT

Patients with co-morbidities such as uncontrolled Diabetes Mellitus, if acquire the COVID-19 have a high chance of developing ARDS which further requires mechanical ventilation. Unfortunately these patients have high mortality rates. This case study reports about a confirmed COVID-19 patient with uncontrolled Diabetes Mellitus along with hypoalbuminemia, later developed ARDS and thus needed assisted mechanical ventilation. As with the use of an anti-Inflammatory drug Ulinastatin, the patients was weaned off from ventilator support on day 6 of the treatment and was discharged eventually after complete recovery. It is presumed and stated on the basis of following case report, is that routine use of Ulinastatin is a potent method of treatment in COVID-19 patients developing ARDS, which may save other patients with similar background.

KEYWORDS

COVID-19, Diabetes Mellitus, ARDS, Ulinastatin, pneumonitic patches

INTRODUCTION

Novel Corona virus19 or commonly abbreviated as COVID-19 becoming a pandemic was inevitable due to its route of transmission and infection rate and if not treated with mechanical ventilation it may worsen the prognosis. No definite pathophysiology or a curative treatment has been suggested.

A male patient of uncontrolled diabetes(Hb 1 A c- 11.5 g/dl) with poor health status having hypoalbuminemia (albumin 1.9g/dl) and confirmed status of COVID-19 treatment facility at Chattrapati Shivaji Subharti Hospital, Meerut, India. The patient required efficient ventilator support. Poor prognosis was explained to family members and the patient was ventilated with immediate effect. In addition to the routine treatment guided by Government of India, a new drug Ulinastatin is advised and administered. This drug works as an anti-inflammatory agent and soothes pain and discomfort while breathing.

As such patients were documented with high mortality rate yet in present case patient started showing recovery after 72 hours. After 6 days of treatment the patient was extubated and saturation was maintained via oxygen support by nasal cannula. The patient was discharged on 14th day of admission, as per health guidelines from local government. Ulinastatin was the only drug that was not routinely used in patients in other COVID treating facilities who are reporting high mortality. With positive outcomes of this case report we may assume this drug to be a bull's eye hitting true target.

LITERATURE REVIEW

It is a well known fact that the ARDS that develops over infective viral pneumonia is largely due to the immune response of the body rather than the primary insult on the alveolocytes by the virus. "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 were 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. Among innate immune cells, we expect the majority to be neutrophils.

Neutrophils can act as double-edged sword as neutrophils can induce lung injury. The majority of the observed infiltrating adaptive immune cells were likely T cells, considering that the significant reduction in circulating T cells was reported. CD8+T cells are primary cytotoxic T cells. These cytotoxic T cells can kill virus but also contribute to lung injury. Circulating monocytes respond to GM-CSF released by these pathological T cells. CD14+CD16+inflammatory monocyte subsets, which seldom exist in healthy controls and were also found at significantly higher percentage in COVID-19 patients. These inflammatory $CD14^{+}$ $CD16^{+}$ monocytes had high expression of IL-6, which likely accelerated the progression of systemic inflammatory response".

Ulinastatin is a drug that is used in cases of SIRS like acute pancreatitis where it limits the inflammatory response and buys time for the normal organ function to recover from the insult. 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 pro-inflammatory cytokines such as IL-1β, IL-10, TNFα have been shown to play an important role in the pathogenesis of AP causing tissue damage and organ dysfunction. In the course of AP, multi-organ 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 the mortality [1]. The intervention in the early stage by targeting inflammatory response may be an effective treatment strategy in the treatment of AP [2].

Furthermore, previous studies [3, 4] have shown that ulinastatin can inhibit the expression of tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), and increase the levels of IL-2 and IL-10. The studies on the mechanism of the anti-inflammatory effect of ulinastatin have mainly been focused on the roles of these cytokines.

Inflammatory cytokines including IL-1, IL-2, IL-4, IL-10 and TNF-α, are released early in the course of SAP leading to the systemic inflammatory response which represents the core problem of SAP. In the recent years, evidence has accumulated that immune reactions and immune cells like CD4+ T cells and Tregs play important roles in the AP pathogenesis [5, 6]. Hence, inhibiting pro-inflammatory mediators [7, 8] and regulating immune reactions [6] are important considerations in the therapy of SAP. It has been confirmed that

ulinastatin prevents the inflammatory response induced by SAP [9], and evidence also indicates that ulinastatin can regulate the immunological function through these special immune cells [10, 11]

Assuming the same pathophysiology to be functional in the ARDS of COVID19 pneumonia Ulinastatin could limit the inflammation of the Alveolar membrane and the systemic inflammatory response there by having a major role in the recovery of patients of severe and critical respiratory symptoms.

CASE PRESENTATION

Patient information

A 54yr Male patient was presented to Subharti Covid-19 facility on 13/05/2020 with worsening breathlessness for 3 days. Patient was tested positive at an authorized government laboratory on 11/05/2020. Patient's history was recorded and he was a non-smoker and non-alcoholic. As patient is Diabetic he was on Tab. Glimiperide 8 mg with Tab.Metformin 1gm(500 mg B.D.)No other relevant past history was noted.

Clinical examination

At the time of admission the oxygen saturation was recorded 90%, it is then increased to 95% on 4 litre oxygen support via nasal prongs. Pulse rate of the patient was recorded 110/min (Tachycardia), Blood pressure was 130/90mm Hg, Respiratory Rate 28/min, RBS was 280 mg/dl. On examination, bilateral air entry was present along with fine inspiratory crepts.

Further diagnostic assessment and Management

Treatment as per government of India guidelines consisted of Tab. Osemeltavir 75mg BD, Tab. Hydroxychloroquine 400mg OD , Tab. Vitamin C 500mg TDS, and Tab. Azithromycin 500mg OD were administered along with medication of diabetes as mentioned above.

On 14/05/2020 the patient reached a saturation of 92% on 6 litre oxygen support and respiratory rate RR 35. By the afternoon RR was 40 and saturation rate reached 88% with drowsiness. Patient was intubated after giving muscle relaxant and shifted to mechanical ventilation. Reports of the patient revealed :- Hb- 12 g/dl, TLC -14000 with increase in neutrophiles, Albumin-1.9 mg/dl and Hb1Ac- 11.5 mmol/mol.

A central venous access by the right jugular route was achieved. Urine of the patient had moderate ketone bodies and RBS was 300 mg/dl. Chest X-ray showed bilateral dense patchy infiltrates.

The treatment of the patient was revised and Inj. Ceftriaxone 1g I/V 12hrly (Antibiotic), Inj. Pantaprazole 40mg I/V 24 hrly (Proton-pump inhibitor), Inj. Insulin Infusion, IV fluids, Injection Low mol weight heparin 0.4mg S/C 24hrly, Inj. Ulinastatin 100,000 I.U in 10ml NS I/V 12hrly. were administered**.** Patient was later sedated due to combination of Atracurium, Fentanyl and Midazolam. Feeding via ryles tube started on next day with an aim of 1500 Kcal and 6 gm protein at 70 ml/hr. Albumin and blood transfusion were also dispensed with the target albumin at 3 g/dl and target Hb 10 g/dl.

On 5th day of intubation weaning of patient started. Patient was carefully extubated by the evening of the 6th day. Patient was later counseled for deep breathing and other respiratory exercises.

INVESTIGATIONS

The primary findings of COVID-19 on Chest radiograph are those of atypical pneumonia or organizing pneumonia.

Chest X Ray on Day 1 shows significant amount of pneumonitic patches (Fig.a,b).

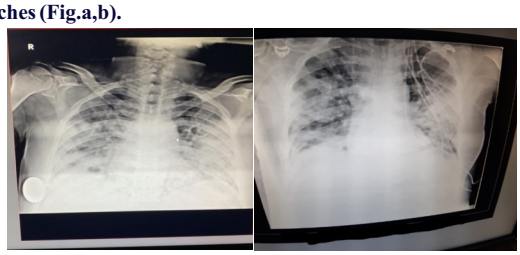
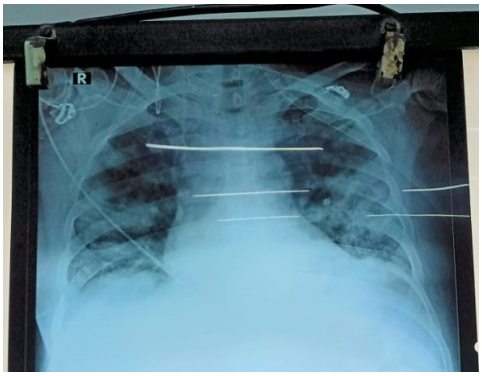


Fig b

Chest X ray on Day 3(On day 2 Ulinastatin was administered)



Chest X ray on Day 8

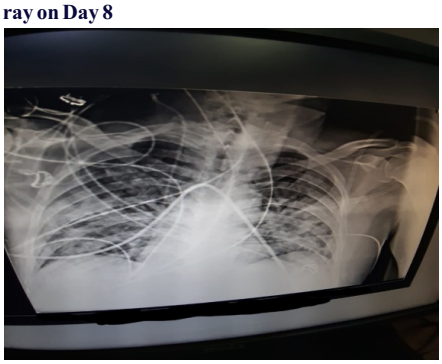
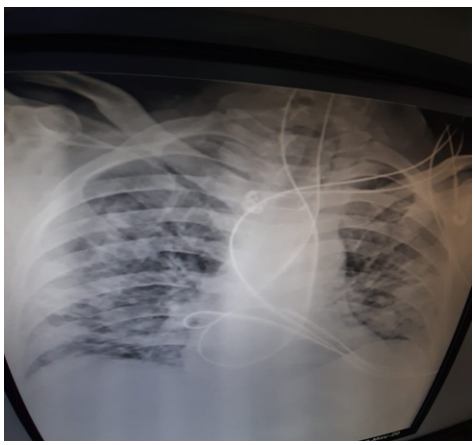
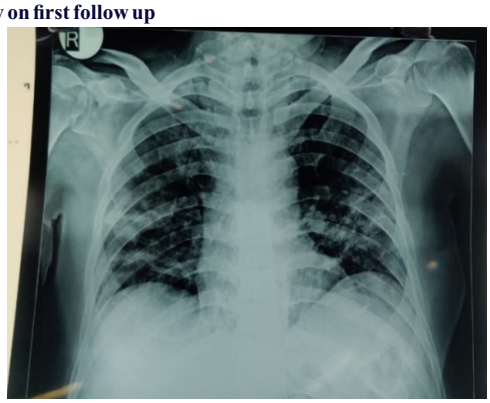


Fig a

Day 18



X-ray on first follow up



CONCLUSION

DIFFERENTIAL DIAGNOSIS

The patient was treated with a diagnosis of COVID-19 type pneumonia with type1 respiratory failure.

TREATMENT

After initial assessment and confirmation of the diagnosis Tab.

Osemeltavir 75mg BD, Tab. Hydroxychloroquine 400mg OD , Tab. Vitamin C 500mg TDS, and Tab. Azithromycin 500mg were started along with antidiabetic medications.

Once the patient deteriorated he was taken up onInj. Ceftriaxone 1g I/V 12hrly, Inj. Pantaprazole 40mg I/V 24 hrly , Inj. Insulin Infusion, IV fluids, Injection Low mol weight heparin 0.4mg S/C 24hrly, Inj. Ulinastatin 100,000 I.U in 10ml NS I/V 12hrly.. Furthermore patient was given mechanical ventilation.

Blood transfusion along with I/V albumin were also given during this period.

Patient was provided with external nutrition via naso-gastric tube to achieve the daily target calorie intake. After extubation patient was provided with chest physiotherapy along with other supportive care.

OUTCOME AND FOLLOW-UP

The patient was discharged after 18 days of hospital stay on 31/05/2020 with stable vitals. He has also been advised for a regular follow up.

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