ROLE OF ULINASTATINS IN COVID 19 ARDS

Emergency Medicine

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ABSTRACT

Covid-19 pandemic has affected huge population with considerable fatality. SARS-CoV-2 virus appears to cause immune dysregulation leading to cytokinin storm and progressive organ damage. Considering the complexity of the disease various immunomodulatory drugs were used along with antiviral agents. Drug like IL6 inhibitors, Steroid had potential adverse effects like Sepsis. Therefore, it is important to identify effective and safe immunomodulatory drug. Ulinastatin is one of the safe immunomodulatory drugs which was previously used in Pancreatitis and Sepsis. Aim of this study is to study the role of Ulinastatins in covid 19 ARDS.

Method: 32 patients were enrolled in the study. 16 patients in group A (Ulinastatins) and 16 in group B (control). Both groups were compared.

Results: Among 32 patients enrolled in the study, group A (Ulinastatins) had 16 patients and group B (control) had 16 patients. Average age in group A is 54.3, group B is 54. Group A had 2 females, 14 males and group B had 3 females,16 males. Group A mortality rate is 18.75% and group B mortality rate is 37.5%. (p=0.238, not significant). Average length of stay among live patents in group A was 11 days and group B was 15.4 days. p value > 0.05 (not significant). In Group A 9 patients out of 12, who required NIV support were weaned. In Group B 2 patients out 10, were weaned from NIV support. (p=0.01, significant). Group A oxygen weaning time was 14 days, group B it was 17 days. (p value - 0.02, significant). Group A- 31% patients required high steroid dose, group B- 62% required high steroid dose for maintain the patients saturations.(P< 0.000005, significant).

Conclusion : Timely initiation of Ulinastatin as an adjuvant drug in moderate to severe disease would help in better prognosis of patient.

KEYWORDS

COVID 19, ARDS, ULINASTATINS

INTRODUCTION: Covid-19 pandemic caused by corona virus 2 (SARS-COV-2) has affected huge population globally and had considerable fatality[1]. It is majorly a respiratory tract infection which may manifest as mild, moderate, severe infection. Nearly 14% develop severe disease requiring hospitalization and 5% need intensive care[2]. So far no effective therapy is available but considering the complexity of disease antivirals, anti-inflammatory and immunomodulatory therapies are tried[3].

SARS COV 2 virus appears to cause immune dysregulation and leading to cytokine storm and progression worsening organ damage especially lung[3]. Therefore, modulation of the immune response or suppression of over reactive cytokine production may play crucial role in severe cases[4,5]. Ulinastatins, immunomodulatory drug can be used as adjuvant therapy in moderate to severe covid 19 virus ARDS[3].

In this study efficacy of Ulinastatins in severe covid 19 ARDS is evaluated.

Study type: Retrograde observational study
Study place: Kamineni hospital (200 bedded) tertiary centre.
Study period: 2 months (May 2021, June 2021)

Method: Among the patients admitted in covid ICU, data of patients with similar age and similar CT severity score were compared.

Inclusion criteria:
*   Age > 18 years
*   CTS (CT chest severity score) $\geq$ 18, covid 19 RT PCR/ RAT (Rapid antigen test) positive
*   SpO^2 levels < 90% on room air

Exclusion criteria:
*   Age <18 years
*   Pregnant patients
*   Patients with cardiogenic pulmonary oedema
*   Patients who received IL6 inhibitors

SEVERITY CLASSIFICATION:
CT SEVERITY SCORING (CT-SS): a semiquantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities based on the area involved. The CT-SS (CT severity score) was calculated based on the extent of lobar involvement.

Each of the five lung lobes was visually scored on a scale of 0–5, 0 indicating no involvement, 1 indicating less than 5% involvement, 2 indicating 5–25% involvement, 3 indicating 26–49% involvement, 4 indicating 50–75% involvement, and 5 indicating more than 75% involvement. The total CTS score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement)[6]

CT SEVERITY SCORE	Severity
<8	Mild
8-17	Moderate
>18	Severe

Data collection:
Patients who were positive for covid 19- RT PCR or rapid antigen, CT severity score $\geq$18 and SpO^2(peripheral oxygen saturation) less than 90% on room air, were enrolled in the study.

Patients categorized into two groups:
1) GROUP A (Ulinastatins group): Patients received Antibiotics, Remdesivir, Steroids, Nebulization, Intravenous fluids, Anti-histaminic drugs. Patients in group A were given additional drug - Ulinastatin 2,00,000 units (diluted in 100 ml normal saline) intravenous infusion over 30 min, every 12th hourly for 5 days to 7 days depending on the oxygenation status.

2) GROUP B (control group) : Patients who have not received Ulinastatins. Patients received Antibiotics, Remdesivir, Steroid, Nebulization, Intravenous fluids, Anti- histaminic drugs.

Antibiotics: Cefoperazone sulbactam/Piperacillin Tazobactam were given for most of the patients. Few patients received Meropenem, Colistin.

Steroids: Dexamethasone or Methyl prednisolone were given. (Dexamethasone 0.75 mg= 4 mg methylprednisolone). Steroid requirement was titrated according to the oxygen saturations.

*   Dexamethasone: Long acting 24 – 72 hours so single dose was given per day. Low dose:$\leq$ 0.15 mg/ kg /day. High dose$\geq$ 0.15 mg/

kg/day.
- Methyl prednisolone: Intermediate acting drug so drug was given 12th hourly.   low dose: 0.5 to1 mg/kg every 12th hourly. High dose: >1 mg/kg every 12th hourly.

Following Parameters were recorded: Name, Age, Symptoms, Comorbidities, day of presentation, SpO_2 levels on room air and oxygen, FiO_2, type of oxygen delivery device, steroid name, steroid dose, CRP, N/L, D Dimers, CT chest severity (CTSS) score, length of hospital stay. Clinical parameters were recorded at the time of admission, every day till patient was discharged. Patients with same age and same CT severity score were compared.

Results:
Among 32 patients enrolled in the study, group A (Ulinastatins) had 16 patients and group B (control) had 16 patients. Average age in group A is 54.3, group B is 54.

Group A had 2 females, 14 males and group B had 3 females and 16 males.

Group A mortality rate is 18.75% and group B mortality rate is 37.5%. (p=0.238, not significant)

In Group A average length of stay in live patents was 11.2+3.9 days and average length of stay in group B was 15.1+5.2 days. p value > 0.05 (not significant)

In Group A 9 out of 12   patient who required NIV support were weaned. In Group B 2 out 10 patient were weaned from NIV support. (p=0.01, significant)

Group A oxygen weaning time was 14+5.6 days, group B it was 16.9+5.4 days. (p value - 0.02, significant).

Group A- 31% patients required high steroid dose, group B- 62% required high steroid dose for maintain the patients saturations. (P< 0.000005, significant)

Discussion:
In covid 19 illness, the incubation and mild stages a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages. In the later stages of the covid-19 infection, the cytokine release syndrome (CRS) causes more severe disease[7]. Severe disease has massive inflammatory cell infiltration and elevated proinflammatory cytokine responses[8,9]. This out of control immune response leads to complications such as Acute Respiratory Disease Syndrome (ARDS), Sepsis and Septic shock, Multiorgan failure[10].

A cytokine profile in covid-19 is characterized by increased Interleukin (IL)-2, IL-6, IL-7, Granulocyte colony-stimulating factor (GCS-f), Interferon-γ (INF-γ) Inducible protein 10, Monocyte chemoattractant protein 1 (MCP-1), Macrophage inflammatory protein 1-α (MIP 1-α), and Tumour necrosis factor-α (TNF-α)[4]. Therefore modulating the immune response is potential therapeutic target in covid 19 patients.

To combat the inflammatory response different type of immunomodulatory drugs like corticosteroids, IL6 inhibitors were used but these drugs had potential adverse effects like sepsis due to immunosupression[11]. Therefore, it is of utmost importance to identify effective therapeutics with high safety. Ulinastatin a immunomodulatory agent, is one such clinically approved drug which does not have potential adverse effects even in high doses[12]. Ulinastatin is broad spectrum Serine protease inhibitor, derived from human urine. Drug is generally used in treatment of Severe Sepsis and Acute Pancreatitis[13]. The anti-inflammatory effects may be considered equivalent to those of steroids without significant suppression of the immune system[14].

A consensus document from China has recommended high-dose Ulinastatin in the prevention and management of cytokine storm in patients with covid-19[15]. further, few of the experts also indicated the use of Ulinastatin in cytokine storm[14].

It is also effective for the treatment of ARDS as observed in various clinical studies. A meta-analysis of 33 randomized controlled trials (RCTS) involving 2,344 patients of ARDS showed that compared to conventional therapy, Ulinastatin was superior in reducing mortality, ventilator-associated pneumonia, duration of mechanical ventilation, length of hospital stay, and increasing the patients oxygenation index[17]. These effects were probably attributable to the effects of Ulinastatin on serum inflammatory markers[18]

Mechanisms of action of Ulinastatins[19]:

Acute pancreatitis: Deactivation of the chain reaction of pancreatic enzymes, such as trypsin, α-chymotrypsin, lipase, amylase, elastase and carboxypeptidase.

Multiple Organ Dysfunction Syndrome(ARDS): Suppression of the activation of polymorphonuclear leukocytes (e.g. Neutrophils), macrophages and platelets.

Sepsis: Inhibition of various serine proteases, such as trypsin, thrombin, chymotrypsin, kallikrein, plasmin, elastase and cathepsin.

Systemic Inflammation: Inhibition of polymorphonuclear leukocytes (e.g. Neutrophils) and pro-inflammatory cytokines including interleukins (e.g. Il-1, il-6 and il-8).

Anti-oxidant effect: Removes oxygen free radicals.

Anticoagulant Activity: Improves microcirculation and tissue perfusion.

Anti-inflammatory, Anti-oxidant effect[20] with additional Anti-coagulant effect[21] (which was found to be defective in covid 19 illness[22], play major role in treatment of severe covid 19 disease. In present study the efficacy of Ulinastatins in patients with severe lung injury due to covid 19 pneumonia was assessed.

In present study it was observed that Ulinastatins were beneficial in covid 19 patients. Group A patients who have received Ulinastatins for 5 to 7 days had lower mortality rate, lower length of hospital stay, lower oxygen weaning duration, majority of patients required lower steroid doses. There was significant radiological opacity clearance in group A.

Limitation of study: Patients enrolled were limited. Further studies required.

Conclusion: Our study revealed that administration of Ulinastatins showed potential benefits in covid 19 patients. As the agent is much safer than other immunomodulatory drugs. Timely initiation of Ulinastatin as an adjuvant drug in moderate to severe disease would help in better prognosis of patient.

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