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Ulinastatin is an immunomodulator in COVID associated cytokine storm: A retrospective observational study

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Abstract

Background: Cytokine storm is the most life-threatening complication of COVID 19. This retrospective observational study explores efficacy of broad-spectrum serine protease inhibitor ulinastatin for treatment of COVID 19 associated cytokine storm.

Materials and Methods: This retrospective observational study evaluated medical records of COVID 19 patients admitted between January 2022 and April 2022 for use of ulinastatin. A total of sixty-six patients were treated with ulinastatin along with standard care and thirty-six patients only with standard care.

Conclusion: The study concludes that the use of ulinastatin is associated with favorable outcome in COVID 19 cytokine storm. Ulinastatin, the advantage over steroid is anti-inflammatory effect but no adverse effect like immunosuppression, hyperglycemia, high blood pressure and psychosis. Inflammatory markers IL6, ferritin, D dimer, CRP, LDH, NLR ratio whose testing kits are freely available are good predictors of cytokine storm.

Introduction

COVID 19 cytokine storm life threatening complication also known as cytokine release syndrome (CRS,) macrophage activation syndrome (MAS) or secondary hemophagocytic lymph histiocytosis (HLH).

Materials and Methods

Present study conducted at Jaypee hospital Noida (India) for treating patients with Covid-19 between January 2022 and April 2022. All patients diagnosed, admitted, and treated for Covid-19 as per guidelines issued by Indian council of medical research (ICMR). The medical records evaluated for use of ulinastatin in COVID 19 patients and were followed for 28 days' post discharge. A total of sixty-six patients treated with ulinastatin along with standard care and thirty-six patients only with standard care. Standard of care in COVID patients included supplement oxygen, steroids, antiviral agents, deep venous thrombosis (DVT) prophylaxis and antibiotics.

Data collection

Data collected from medical records included clinical information, medication, laboratory results

and radiological examinations records. Patient characteristics data collected included age, sex, symptoms, and comorbidities.

Ulinastatin group (UG)

The criteria of treating team for giving ulinastatin in confirmed COVID positive patient were presence of any of two of three following criteria which predict severe COVID disease:

Two or more comorbidities

At time of admission SPO2<92% on room air or RR >30 breaths/ min Neutrophil/lymphocyte ratio (NLR) >4.4. The initial dose of ulinastatin was 200,000 IU every 12 h for 5 days. Ulinastatin was diluted with 50 ml normal saline and administered as infusion over 30 min.

Exclusion criteria

Age < 18 years, Pregnant woman, Lactating women, Hypersensitivity to the drug.

Control group

All COVID confirmed cases between January 2022 and April 2022 who did not fulfil above criteria were not given ulinastatin and taken as control for the study.

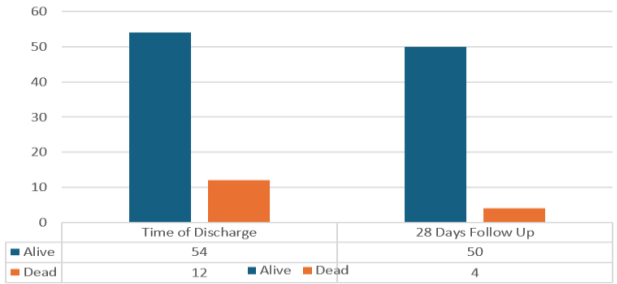

Figure 1: Bar graph depicting hospital discharge rate and 28 days follow up survival.in Ulinastatin group.

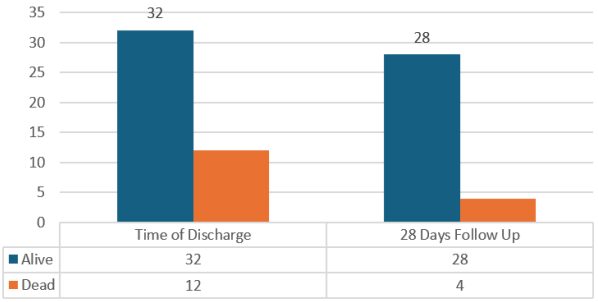

Figure 2: Bar graph depicting hospital discharge rate and 28 days follow up survival for cytokine storm in Ulinastatin group.

Cytokine storm criteria:

1. Organ failure like ARDS, acute kidney injury, liver failure, transaminases, or myocarditis
2. Interleukin 6 ten times the upper limit of normal i.e., 70 pg. /ml

Statistical analysis:

All calculations performed using computer programs Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) and Statistical Package for the Social Science (SPSS) version 21.0(IBM Corp., Armonk, NY).

Result

The mean APACHE score in Ulinastatin group (mean-18.45 ± 8.28) was more than control group (mean-9.44 ±4.84) [Mann Whitney U test (p<0.001)]. Pre and post mean of IL6 and CRP are 116 vs 43.74 and 12.57 vs 5.94 respectively in control and ulinastatin group. Before and after administration of Ulinastatin, The median of D

dimer, ferritin and LDH were 1021 vs 476.5, 627vs 397 and 322.85 vs 207.05 respectively. Ulinastatin may decrease inflammatory markers like IL6, ferritin, D dimer, CRP and LDH. (Wilcoxon signed rank test. p value <0.05). NLR showed positive correlation (0.364) with cytokine storm. (p value=0.003). The mean NLR was significantly higher in patients with cytokine storm than in patients without cytokine storm. (Mean NLR 13.23 vs 6.20) (Mann Whitney U test, p value =0.003) . Thus, NLR was found to be an important indicator of severity of COVID infection and cytokine storm. The mean of IL6, ferritin, D dimer, CRP and LDH in cytokine storm and noncytokine storm were 155.86 and 35.39, 1508 and 552.05, 3910 and 1111.77,14.42 and 8.96, 564 and 241.06 respectively [Wilcoxon signed ranks test (p value<0.005)]. In Ulinastatin group hospital discharge rate was 81.81 % and follow up 28 days' survival rate was 92.59% [figure-1].In patients, who had COVID associated cytokine storm and treated with Ulinastatin, hospital discharge rate was 72.7 % and follow up 28 days' survival rate was 87.5% [Figure 2]. In Ulinastatin group, 44 patients had cytokine storms of which forty patients had ARDS along with cytokine storms. Lung is the most common organ dysfunction (ARDS) in COVID associated with cytokine storm.

Discussion

In cytokine storm, there are increased release of proinflammatory cytokines leading to a dysregulated and hyperactive immune response causing organ dysfunction like secondary HLH. The present study observed high level of ferritin, D-dimer, CRP and LDH in patients cytokine storm patients as compared to patient without it. Ferritin is an important indicator of cytokine storm in COVID 19 patients.[1] D-dimer elevated levels are important, and persistent elevation confers to severe disease is also shown in previous studies.[2] CRP, non-specific acute phase reactant synthesized by the liver in response to IL-6 is elevated in infection or inflammation. Study shows elevated CRP associated with more severe disease and cytokine storm. CRP>40 mg/L was associated with increased mortality in COVID 19 infection.[3] One study concluded that CRP in COVID 19 infection strongly correlated with systemic inflammation and associated with venous thromboembolism, acute kidney injury, critical illness, and in-hospital mortality.[4] Elevated LDH was associated with severe COVID 19 infection, respiratory failure and cytokine storm as evident in present study.[5] NLR showed positive correlation with cytokine storm. Another study also showed high NLR in severe cases.[6] Present study indicates that COVID 19 cytokine predictor model based on IL6, ferritin, D dimer, CRP, LDH might be helpful in early recognition and treatment of immunologic life- threatening complication of COVID 19 associated cytokine storm. Ulinastatin showed to decrease inflammatory markers like IL6, ferritin, D dimer, CRP, LDH in this study. Comparable results were seen in Meta-analysis demonstrating significant reduction in inflammatory markers levels in TNF-α, IL-1β, IL-6, and IL-8 in Ulinastatin group.[6] The most common organ dysfunction in COVID associated cytokine storm is ARDS. One meta-analysis of thirty-three randomized controlled trials involving 2,344

demonstrated reduced mortality, ventilator-associated pneumonia, mechanical ventilation duration, length of hospital stays, and increased patients' oxygenation index in Ulinastatin group as compared to control.[7] COVID-19 uses ACE2 receptor for entry in host cells and host cell protease TMPRSS2 necessary for spike protein receptor priming for effective attachment to the ACE2 receptor. Serine protease inhibitor prevents effective binding of COVID-19 to ACE2 receptor by acting on host cell protease TMPRSS2.[8] A study demonstrated that Camostat (serine protease inhibitor) may prevent SARS-CoV 2 spread.[9] Nafamostat (serine protease inhibitor) inhibits MERS-CoV S protein-mediated membrane fusion.[10] Hence broad-spectrum serine protease inhibitor like Ulinastatin was used for COVID 19 cytokine storm. The 2019 Shanghai Expert consensus recommended broad-spectrum serine protease inhibitors in the treatment of COVID-19.[11] Recovery trial showed that oral or intravenous dexamethasone (at a dose of 6 mg once daily for up to 10 days) anti-inflammatory effect resulted in lower 28-day mortality among those who were received oxygen alone or invasive mechanical ventilation.[12] The advantage of ulinastatin is anti-inflammatory effects but no adverse effect associated with steroids like immunosuppression, hyperglycemia, high blood pressure and psychosis.

Conclusion

Inflammatory markers IL6, ferritin, D dimer, CRP, LDH, N/L ratio whose testing kits are freely available may be good predictors of cytokine storm. We propose for larger sample size randomized control trial to prepare a cytokine predictor model based on this retrospective observational study which can lead to early diagnosis and treatment of cytokine storm and better prognosis. Role of Ulinastatin should also be studied further in patient with COVID 19 in regards to improvement in organ dysfunction, hospital discharge and 28 days survival rate.

Source of Funding

None.

Conflict of Interest

None.

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