Effect of Urinary Trypsin Inhibitor (Ulinastatin) Therapy in COVID-19

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ABSTRACT

Purpose: End-organ damage in coronavirus disease-2019 (COVID-19) is linked to “cytokine storm” and excessive release of inflammatory mediators. Various novel therapies have been used in COVID-19 including urinary trypsin inhibitor therapy. This study explores the efficacy of ulinastatin in COVID-19.

Materials and methods: We retrieved the medical records of patients admitted during one month and did a propensity score analysis to create matched treatment and control groups. We analyzed these groups and the outcomes were presented with appropriate statistics. Survival curve was prepared to compare the survival effect of ulinastatin therapy at the end of hospitalization, among both the groups.

Results: A total of 736 patients were admitted, and after adjusting the data with propensity score matching, 55 cases were selected by the system. On the final outcome analysis, we found that intensive care unit (ICU) length of stay [median (interquartile range) days 3 (3.5–7.8) vs 2 (0–4); p-value 0.28] in control vs intervention groups, and in hospital mortality (odds ratio: 0.491, CI 95%: 0.099–2.44, p-value 0.435) were not statistically different among the groups. In survival plot analysis also, there was no statistical difference (p-value 0.414) among both the groups.

Conclusion: In this retrospective study, we conclude that the final outcome of the ICU length of stay, and overall, in hospital mortality were not different among both the groups. Hence, adequately powered randomized control trials are urgently required to confirm any benefit of ulinastatin therapy in COVID-19 treatment.

Keywords: Anti-inflammatory therapy, COVID-19, Cytokine storm, Immune modulation therapy, Retrospective study, Ulinastatin, Urinary trypsin inhibitor therapy.

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) pandemic has already made an indelible mark on human history, by its sheer magnitude and effect on global human health. The disease typically has a very high mortality in its advanced stages and multisystem involvement is remarkable. Moderate and severe COVID-19 cases are characterized by “cytokine storm” and excessive release of inflammatory mediators. However, differences among other cytokine-releasing syndromes and COVID-19 could not be established. But due to lack of concrete evidence, a large number of physicians resorted to various immune modulation, and anti-inflammatory therapies for the treatment of moderate and severe COVID-19. Urinary trypsin inhibitor (ulinastatin) therapy was one such therapy.

Ulinastatin has been used with limited success in conditions with raised inflammatory markers and systemic inflammation (like acute respiratory distress syndrome (ARDS), pancreatitis, sepsis, burns, etc.). Citing similar pathophysiology behind the organ damage related to COVID-19, experts recommended a daily dose of one million units of ulinastatin for the prevention and treatment of cytokine storm and hypoxia caused by COVID-19. However, definite evidence for ulinastatin use in COVID-19 is still lacking. Hence in this study, we intended to explore the efficacy of ulinastatin in COVID-19.

MATERIALS AND METHODS

This was a single-center retrospective observational study to explore the effect of urinary trypsin inhibitor (ulinastatin) therapy on final outcome of death and intensive care unit (ICU) length of stay in COVID-19 patients. For this study, we retrieved patient information from the medical records and included all adult patients admitted to our institute during the month of November 2020, with a clinical and microbiological confirmed diagnosis of COVID-19. All the patients were categorized into three clinical categories (mild, moderate, and severe) at the time of admission as per the criteria laid down by the local guidelines.
Some of these patients were treated with urinary trypsin inhibitor therapy on compassionate ground and as a desperate measure, apart from other standard treatment protocols (which included antiviral remdesivir, prophylactic/therapeutic anticoagulation, low dose and short duration of steroid therapy, and other supportive care as appropriate). The decision to start urinary trypsin therapy was entirely based on the discretion of treating consultants and patients or substitute decision-makers on behalf of the incapacitated patients.

The physicians used urinary trypsin inhibitors according to our institutional protocol, while considering the physiological plausibility of use. They considered the various combinations of C-reactive protein (CRP) levels on admission, maximum CRP levels, D-dimer levels on admission, maximum D-dimer level, computed tomographic (CT) severity score at admission, and/or use of oxygen therapy as per case-by-case preferences. Urinary trypsin inhibitors were used in a standard dose of 10 lakh units/per day for three days in continuous infusion as per our institutional protocol.5

We collected all the available epidemiological, laboratory, clinical, and pharmacological data of these patients on standard research forms. These data were archived in a master chart and further used for analysis.

Ethical clearance for this study was granted by the local institutional ethics committee. As this study was retrospective in design and data were based on the exploration of medical records only, consent from the participants was not obtained. Our team did not receive any grant or financial aid of any kind for this project and the entire study was self-funded by the researchers.

**Statistical Analysis Plan**

We did an analysis of acquired data systematically as planned on a priory basis. The data were checked for outliers, and values are presented as mean ± standard deviation, median (interquartile range, IQR) for continuous variables, and as numbers and percentages for categorical variables as found appropriate during analysis. Initially, we did a univariate analysis of the prepared retrospective treatment and control group. We used the Mann–Whitney U test, Chi-square test, or Fisher’s exact test, and other comparable tests to check for the significance of variables among the groups.

We further adjusted the data by doing a propensity score analysis to match, “CRP on admission, maximum CRP levels, D-dimer on admission, maximum D-dimer level, CT severity score at admission, and use of oxygen therapy” variables. Thus, we selected cases where the urinary trypsin inhibitor treatment allocation propensity was 50% or above based on matched characteristics, and we created matched treatment and control groups. These propensity scores matched groups were analyzed for significance among various variables and derived outcome data were presented as odds ratio and confidence interval (CI) 95%. Kaplan–Meier curves were prepared to compare the survival effect of urinary trypsin inhibitor therapy at the end of hospitalization, among matched treatment and control groups. All the tests were two-tailed and p-value <0.05 was considered as significant. All the statistical analyses were done using SPSS (version 25.0, IBM SPSS Inc., Chicago, IL, USA) unless otherwise indicated. Tabulation and final documentation were done using MS Office software (MS office 2019, Microsoft Corp, WA, USA).

**Results**

During the study period, our institute admitted 736 patients diagnosed with COVID-19 (Flowchart 1, details of the study population). We evaluated the medical records of these patients and could include a total of 658 cases, as the crucial intervention-related data were not available in the records, or other than the
Table 1: Univariate analysis of observed variables of unmatched treatment and control groups

| Continuous variables | Not treated with urinary trypsin inhibitor therapy | Treated with urinary trypsin inhibitor therapy | p value |
|----------------------|---------------------------------------------------|---------------------------------------------|---------|
|                      | N | Missing | Valid | Median | Q1 | Q3 | Percentiles | N | Missing | Valid | Median | Q1 | Q3 | Percentiles | p value |
| AGE                  | 456 | 0 | 58 | 47 | 68 | 202 | 0 | 63.5 | 55 | 71 | 0 |
| Duration of hospital stay | 456 | 0 | 6.5 | 5 | 9 | 202 | 0 | 8 | 6 | 11 | 0 |
| Duration of symptoms before admission | 434 | 22 | 3 | 3 | 4 | 186 | 16 | 3 | 3 | 5 | 0.2 |
| CRP on admission     | 402 | 54 | 32 | 11.35 | 72.17 | 178 | 24 | 65.45 | 29.35 | 196.17 | 0 |
| CRP maximum          | 403 | 53 | 33 | 11.7 | 73.3 | 178 | 24 | 76.65 | 33.65 | 210.77 | 0 |
| IL-6 on admission    | 261 | 195 | 9.4 | 3.52 | 29.15 | 116 | 86 | 25 | 6.8 | 62 | 0 |
| IL-6 maximum         | 264 | 192 | 9.95 | 3.52 | 29.15 | 116 | 86 | 27.8 | 8.92 | 73.17 | 0 |
| D-dimer on admission | 363 | 93 | 282 | 216 | 501 | 175 | 27 | 325 | 240 | 825 | 0.003 |
| D-dimer maximum      | 363 | 93 | 292 | 226 | 555 | 175 | 27 | 370 | 254 | 1085 | 0 |
| Ferritin on admission| 330 | 126 | 227.5 | 111.45 | 432 | 170 | 32 | 343.5 | 176.55 | 670.72 | 0 |
| Ferritin maximum     | 330 | 126 | 237.75 | 117.5 | 439.25 | 170 | 32 | 377.5 | 219.5 | 788 | 0 |
| CT severity score    | 222 | 234 | 12 | 8 | 17 | 88 | 114 | 16 | 12 | 19 | 0 |
| Duration of ICU stay | 446 | 10 | 0 | 0 | 0 | 187 | 15 | 0 | 0 | 5 | 0 |

| Categorical variables | Series | Not treated with urinary trypsin inhibitor therapy | Treated with urinary trypsin inhibitor therapy | p value |
|-----------------------|--------|---------------------------------------------------|---------------------------------------------|---------|
|                       |        | N | % | Missing data | N | % | Missing data | p value |
| Gender                | Male   | 326 | 71.5 | 0 | 150 | 74.3 | 0 | 0.46 |
|                       | Female | 130 | 28.5 | 0 | 52 | 25.7 | 0 | 0.46 |
| Symptomatology        | Asymptomatic | 8 | 18 | 5 (1.1%) | 0 | 0 | 2 (1.0%) | 0.008 |
|                       | ILI    | 144 | 31.6 | 41 | 20.3 | 0 | 0 | 2 (1.0%) | 0.008 |
|                       | ARI    | 295 | 64.7 | 158 | 78.2 | 0 | 0 | 2 (1.0%) | 0.008 |
|                       | AGE    | 4 | 0.9 | 1 | 0.5 | 0 | 0 | 2 (1.0%) | 0.008 |
| Severity of disease at admission | Mild | 95 | 20.8 | 66 (14.5%) | 61 | 30.2 | 10 (5.0%) | 0 |
|                       | Moderate | 60 | 13.2 | 88 | 43.6 | 0 | 0 | 2 (1.0%) | 0.008 |
|                       | Severe | 235 | 51.5 | 43 | 21.3 | 0 | 0 | 2 (1.0%) | 0.008 |
| Co-morbidities        | DM     | 185 | 40.57 | 0 | 96 | 47.52 | 0 | 0.81 |
|                       | HTN    | 170 | 37.28 | 96 | 47.52 | 0 | 0 | 0.81 |
|                       | CAD    | 28 | 6.14 | 23 | 11.38 | 0 | 0 | 0.81 |
|                       | CKD    | 22 | 4.82 | 9 | 4.45 | 0 | 0 | 0.81 |
|                       | Resp illness | 14 | 3.07 | 3 | 1.48 | 0 | 0 | 0.81 |
|                       | Neurological illness | 11 | 2.41 | 4 | 1.98 | 0 | 0 | 0.81 |
|                       | Malignancy | 2 | 0.4 | 4 | 1.98 | 0 | 0 | 0.81 |
|                       | Other | 32 | 7.07 | 16 | 7.92 | 0 | 0 | 0.81 |
protocolized doses were used in the remaining 78 cases. These 658 cases were evaluated for crude univariate analysis among the intervention and control groups, details of which have been provided (Table 1). These data suggest that all the continuous study variables such as age (p-value 0.00), duration of hospital stay (p-value 0.00), CRP levels on admission (p-value 0.00), maximum CRP levels (p-value 0.00), interleukin (IL)-6 levels on admission (p-value 0.00), maximum IL-6 levels (p-value 0.00), D-dimer levels on admission (p-value 0.003), maximum D-dimer levels (p-value 0.00), ferritin levels on admission (p-value 0.00), maximum ferritin levels (p-value 0.00), CT severity score at admission (p-value 0.00), and duration of ICU stay (p-value 0.00) were statistically different among the groups. There was also statistical difference among the groups on categorical variables like the severity of disease at admission (p-value 0.00), Charlson’s co-morbidity index score (p-value 0.01), anti-viral therapy uses (p-value 0.00), anticoagulation therapy uses (p-value 0.003), corticosteroid therapy uses (p-value 0.002), IL-6 inhibitor therapy (tocilizumab) use (p-value 0.00), oxygen therapy use (p-value 0.00), ventilation support (p-value 0.00), need for ICU stay (p-value 0.00), and in-hospital mortality (p-value 0.00).

After adjusting the data with propensity score matching, a total of 55 cases were selected by the system based on six variables (Flowchart 1, details of the study population). These were further divided into control (n = 23) vs intervention arms (n = 32).

We performed a univariate analysis in this matched sample (Table 2) and found that there was a difference in duration of symptoms before admission (p-value 0.048), IL-6 levels on admission (p-value 0.015), and maximum IL-6 levels among the groups (p-value 0.015), and all other relevant variables were well matched. On the final outcome analysis, we found that ICU length of stay [median (IQR) days 3 (3.5–7.8) vs 2 (0–4) p-value 0.28] in control vs intervention groups and in-hospital mortality (odds ratio: 0.491, CI 95%: 0.099–2.44, p-value 0.435) were not statistically different among the groups (Table 2).

We did survival plot analysis and found that there was no statistical difference (p-value 0.414) on the cumulative probability of survival among both the groups (Fig. 1, the cumulative probability of patient survival).

**Discussion**

Coronavirus disease-2019 (COVID-19) is truly a novel disease and a standard management approach based on limited evidence has been provided by the regional and global healthcare authorities.\(^1\text{7—19}\) COVID-19-related organ damage is largely attributed to the cytokine storm caused during the disease.\(^4\text{5,10—20}\)

Ulinastatin use has been advocated by the expert panels to counter the inflammatory surge; however, no clinical studies are available to compare the evidence so far.\(^5,16\) In our retrospective study, we found that ICU length of stay [median (IQR) day 3 (3.5–7.8) vs day 2 (0–4) p-value 0.28] in control vs intervention groups and in-hospital mortality (odds ratio: 0.491, CI 95%: 0.099–2.44, p-value 0.435) were not statistically different among the groups (Table 2).

In several previous studies, ulinastatin was proven useful in other illnesses (like burns and sepsis) in reducing the inflammatory load and subsequently improving the final outcome.\(^21,22\) A recent meta-analysis included 11 eligible studies with 399 pancreatitis patients. It showed that the serum levels of CRP, IL-6, and tumor necrosis factor (TNF)-α were evidently decreased (CRP: Standardized mean difference (SMD) = –2.697, 95% CI = –4.399 to –0.994, p-value 0.002; IL-6: SMD = –5.268, 95% CI = –9.850 to –0.687,
Table 2: Univariate analysis of observed variables among the Matched treatment and control groups of urinary trypsin inhibitor therapy (ulinastatin)

| Continuous variables | Not treated with Urinary trypsin inhibitor therapy (n = 23) | Treated with urinary trypsin inhibitor therapy (n = 32) |
|----------------------|------------------------------------------------------------|-------------------------------------------------------|
|                      | N  | Median | Q1 | Q3 | N  | Median | Q1 | Q3 | p value |
| Age                  | 23 | 0      | 56 | 42 | 65 | 32 | 0      | 56 | 49.25 | 70 | 0.505 |
| Duration of hospital stay | 23 | 0      | 10 | 7  | 13 | 32 | 0      | 10 | 7     | 10 | 0.871 |
| Duration of symptoms before admission | 23 | 0      | 5  | 3  | 8  | 30 | 2      | 3  | 3     | 5  | 0.048 |
| CRP levels on admission | 23 | 0      | 80.9 | 66.1 | 206 | 32 | 0      | 197.9 | 44.55 | 242.25 | 0.207 |
| Maximum CRP levels | 10 | 13     | 8.85 | 4.45 | 22.85 | 20 | 12     | 42.25 | 11.25 | 95.52 | 0.015 |
| IL-6 levels on admission | 23 | 0      | 149.5 | 72  | 212 | 32 | 0      | 210.4 | 86.92 | 246.25 | 0.147 |
| Maximum IL-6 levels | 10 | 13     | 8.9  | 4.5 | 22.9 | 20 | 12     | 42.3  | 11.3  | 95.5  | 0.015 |
| D-dimer levels on admission | 23 | 0      | 500 | 287 | 1803 | 32 | 0      | 595.5 | 317.3 | 1739 | 0.865 |
| Maximum D-dimer levels | 23 | 0      | 618 | 342 | 2600 | 32 | 0      | 606  | 317.3 | 2318.8 | 0.597 |
| Ferritin levels on admission | 18 | 5      | 393 | 265.8 | 791 | 29 | 3      | 432  | 227.7 | 852.2 | 0.93 |
| Maximum Ferritin levels | 18 | 5      | 393 | 265.8 | 878.3 | 29 | 3      | 502  | 314.5 | 852.2 | 0.678 |
| CT severity score at admission | 23 | 0      | 19  | 17 | 21 | 32 | 0      | 19   | 16   | 21    | 0.745 |
| Duration of ICU stay | 22 | 1      | 3.5 | 0  | 7.8 | 30 | 2      | 2    | 0    | 4     | 0.28 |

| Categorical variables | Not treated with urinary trypsin inhibitor therapy | Treated with urinary trypsin inhibitor therapy |
|-----------------------|--------------------------------------------------|---------------------------------------------|
|                       | N (%) | Missing data | N (%) | Missing data | p value |
| Gender                | Male   | 18 | 78.3 | 0 | 28 | 87.5 | 0 | 0.46 |
|                       | Female | 5  | 21.7 | 0 | 4  | 12.5 | 0 | 0.158 |
| Severity of disease at admission | Mild | 8 | 34.8 | 0 | 10 | 31.3 | 0 | 0.517 |
|                       | Moderate | 14 | 60.9 | 0 | 19 | 59.4 | 2 | 3.6% |
|                       | Severe | 1  | 4.3  | 0 | 1  | 3.1  | 0 | 0.7 |
| Charlson's Co-morbidity index | 0 | 2 | 8.7 | 0 | 4 | 12.5 | 0 | 0.158 |
|                       | 1 | 6 | 26.1 | 0 | 7 | 21.9 | 0 | 0.157 |
|                       | 2 | 7 | 30.4 | 0 | 4 | 12.5 | 0 | 0.157 |
|                       | 3 | 5 | 21.7 | 0 | 6 | 18.8 | 0 | 0.157 |
|                       | 4 | 1 | 4.3  | 0 | 9 | 28.1 | 0 | 0.157 |
|                       | 5 | 0 | 0    | 0 | 1 | 3.1  | 0 | 0.157 |
|                       | 6 | 2 | 8.7  | 0 | 1 | 3.1  | 0 | 0.157 |
| Anti-viral therapy | 19 | 82.6 | 0 | 31 | 96.9 | 0 | 0 | 0.149 |
| Anticoagulation therapy | 22 | 95.7 | 1 | 4.3% | 30 | 93.8 | 0 | 0 | 0.141 |
| Corticosteroid therapy | 23 | 100 | 0 | 32 | 100 | 0 | NA | 0 | 0.141 |
| IL-6 inhibitor therapy (tocilizumab) | 22 | 95.7 | 0 | 31 | 96.9 | 1 | 1 | 0 | 0.141 |
| Oxygen therapy | 14 | 60.9 | 0 | 19 | 59.4 | 0 | 0 | 0.91 |
| ICU stay | 4 | 17.4 | 0 | 4 | 12.5 | 0 | 0.7 |
| Ventilation support | None | 17 | 73.9 | 2 | 8.7 | 22 | 68.8 | 6 | 18.8 | 0.25 |
|                       | Non-invasive | 1 | 4.3 | 0 | 0 | 0 | 0 | 0 | 0.25 |
|                       | Invasive | 3 | 13 | 4 | 12.5 | 0 | 0.25 |
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Outcome comparison of unmatched and matched groups

|                       | Crude analysis (n = 658) | Propensity matched analysis (n = 55) |
|-----------------------|--------------------------|-------------------------------------|
|                       | Odds ratio               | Lower limit of CI                   | Upper limit of CI | p value | Odds ratio               | Lower limit of CI | Upper limit of CI | p value |
| Overall, in hospital mortality | 4.65 | 2.64 | 8.17 | <0.000 | 0.491 | 0.999 | 2.446 | 0.435 |
| ICU length of stay     | 1.242 | 1.164 | 1.324 | <0.000 | 1.073 | 0.927 | 1.241 | 0.28 |

ARL, acute respiratory illness; AGE, acute gastroenteritis; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; IQR, inter quartile range; ILI, influenza like illness; ICU, intensive care unit

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Ulinastatin use was proven beneficial in many other such conditions.13,15,23–26 In the limited sense of our study, we were not able to confirm any such benefit on final outcomes with the use of ulinastatin therapy in addition to usual care protocol in COVID-19. However, due to the retrospective nature of this study and the paucity of

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Fig. 1: Cumulative probability of patient survival among the matched urinary trypsin inhibitor treatment and control group

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p-value 0.024; TNF-α: SMD = −5.666, 95% CI = −11.083 to −0.249, p-value 0.040) after using ulinastatin. But still, the use of ulinastatin could not be translated into improvement of the final outcome.13 Another meta-analysis of 33 randomized control trials (RCTs) involving 2,344 patients in ARDS patients, showed that ulinastatin treatment significantly reduced mortality (RR = 0.51, 95% CI: 0.43 to 0.61), the occurrence of ventilator-associated pneumonia rate (RR = 0.50, 95% CI: 0.36 to 0.69), and shortening duration of mechanical ventilation (SMD = −1.29, 95% CI: −1.95 to −0.80), hospital stay (SMD = −1.70, 95% CI: −2.63 to −0.77), and ulinastatin significantly improved oxygenation index, respiratory rate, and serum inflammatory factors (TNF-α, IL-1β, IL-6, IL-8).13 Ulinastatin use was proven beneficial in many other such conditions.13,15,23–26

In the limited sense of our study, we were not able to confirm any such benefit on final outcomes with the use of ulinastatin therapy in addition to usual care protocol in COVID-19. However, due to the retrospective nature of this study and the paucity of
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data, comments related to possible adverse reactions, safety, and toxicities of the drug could not be made.

**Strength and Limitations**

In this retrospective study, we could include a number of patients who have received ulinastatin therapy on compassionate grounds. Due to the retrospective nature of this study, we had a paucity of many data and hence comments related to possible adverse reactions, safety, and toxicities of the drug could not be made. However, this is one of the leading efforts to explore the efficacy of much debated and popularized “ulinastatin therapy” in the management of COVID-19. In its limited sense, this study provides vital data on the efficacy of urinary trypsin inhibitor therapy and warrants the need for RCTs before making any hyped claims of its benefit.

**Conclusion**

In this retrospective study, we conclude that after a propensity score-matched analysis of the data acquired retrospectively in our institute, the final outcome of the ICU length of stay, and overall, in-hospital mortality was not different among the urinary trypsin inhibitor-treated and non-treated patients. Most of the patients were treated with the standard institutional protocol for COVID-19 care which is based on regional official guidance (which includes antiviral remdesivir, prophylactic/therapeutic anti-coagulation, low dose, and short duration of steroid therapy and other supportive care as appropriate). Hence, adequately powered RCTs are urgently required to confirm any benefit of urinary trypsin inhibitor therapy in COVID-19.

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