ORIGINAL ARTICLE

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.[1] Moderate and severe COVID-19 cases are characterized by "cytokine storm" and excessive release of inflammatory mediators.[2,3] However, differences among other cytokine-releasing syndromes and COVID-19 could not be established.[4,5] 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.[6–9] 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.).[10–15] 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.[6,16] 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

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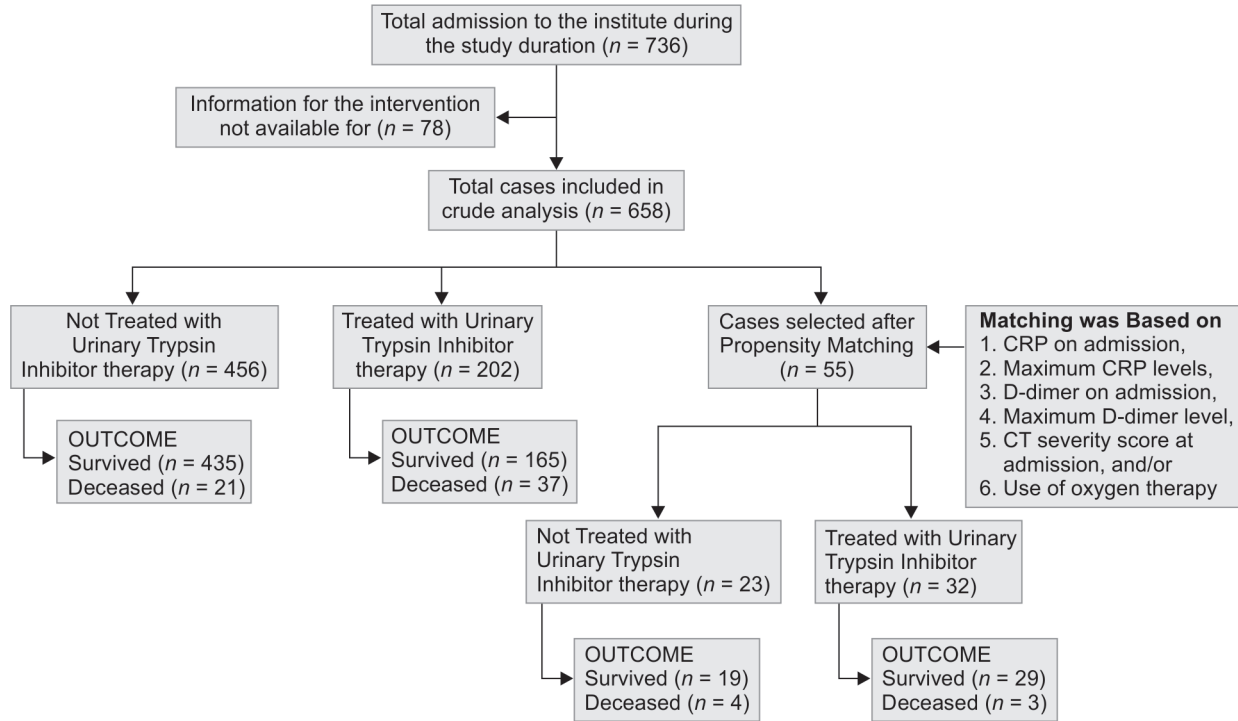
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on final outcome of death and intensive care unit (ICU) length of stay in COVID-19 patients. For this study, we retrieved patient information from the medical records and included all adult patients admitted to our institute during the month of November 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.[17]

Flowchart 1: Distribution of study population according to urinary trypsin inhibitor therapy

Total admission to the institute during the study duration (n = 736)

Information for the intervention not available for (n = 78)

Total cases included in crude analysis (n = 658)

Not Treated with Urinary Trypsin Inhibitor therapy (n = 456)

OUTCOME
Survived (n = 435)
Deceased (n = 21)

Treated with Urinary Trypsin Inhibitor therapy (n = 202)

OUTCOME
Survived (n = 165)
Deceased (n = 37)

Cases selected after Propensity Matching (n = 55)

Matching was Based on
1. CRP on admission,
2. Maximum CRP levels,
3. D-dimer on admission,
4. Maximum D-dimer level,
5. CT severity score at admission, and/or
6. Use of oxygen therapy

Not Treated with Urinary Trypsin Inhibitor therapy (n = 23)

OUTCOME
Survived (n = 19)
Deceased (n = 4)

Treated with Urinary Trypsin Inhibitor therapy (n = 32)

OUTCOME
Survived (n = 29)
Deceased (n = 3)

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.[6]

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* | | | *Percentiles* | | *N* | | | *Percentiles* | | |
	Valid	*Missing*	*Median*	*Q1*	*Q3*	*Valid*	*Missing*	*Median*	*Q1*	*Q3*	
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	233.75	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* | | *Missing data* | *Treated with urinary trypsin inhibitor therapy* | | *Missing data* | *p value* |
		N	*%*	*N (%)*	*N*	*%*	*N (%)*	
Gender	Male	326	71.5	0	150	74.3	0	**0.46**
	Female	130	28.5		52	25.7		
Symptomatology	Asymptomatic	8	18	5 (1.1%)	0	0	2 (1.0%)	**0.008**
	ILI	144	31.6		41	20.3		
	ARI	295	64.7		158	78.2		
	AGE	4	0.9		1	0.5		
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		
	Severe	235	51.5		43	21.3		
Co-morbidities	DM	185	40.57	0	96	47.52	0	**0.81**
	HTN	170	37.28		96	47.52		
	CAD	28	6.14		23	11.38		
	CKD	22	4.82		9	4.45		
	Resp illness	14	3.07		3	1.48		
	Neurological illness	11	2.41		4	1.98		
	Malignancy	2	0.4		4	1.98		
	Other	32	7.07		16	7.92		

Charlson's Co-morbidity index	0	85	18.6	0	19	9.4	0	**0.01**
	1	87	19.1		31	15.3		
	2	90	19.7		39	19.3		
	3	103	22.6		49	24.3		
	4	61	13.4		47	23.3		
	5	19	4.2		12	5.9		
	6	9	2		4	2		
	7	2	0.4		1	0.5		
Remdesivir		375	82.2	12 (2.6%)	198	98	2 (1.0%)	0
Anticoagulation therapy		418	91.7	4 (0.9%)	199	98.5	0	0.003
Corticosteroid therapy		435	95.4	21 (4.6%)	202	100	0	0.002
IL-6 inhibitor therapy (tocilizumab)		9	2	4 (0.9%)	28	13.9	22 (10.9%)	0
Oxygen therapy		126	27.6	51 (11.2%)	144	71.3	8 (4.0%)	0
ICU stay		76	16.7	0	106	52.5	0	0
Ventilation support		28	6.1	0	45	22.3	0	0
Mode of ventilation support	None	417	91.4	10 (2.2%)	136	67.3	20 (9.9%)	0
	Non-invasive	7	1.5		11	5.4		
	Invasive	22	4.8		35	17.3		
Outcome	Survived	435	95.4	0	165	81.7	0	0
	Deceased	21	4.6		37	18.3		

AGE, acute gastroenteritis; ARI, acute respiratory illness; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; ILI, influenza like illness; IQR, inter qua rtile range

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.[17–19] COVID-19-related organ damage is largely attributed to the cytokine storm caused during the disease.[4,5,10,20] 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.[6,16] 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 ~ –0.994, p-value 0.002; IL-6: SMD = –5.268, 95% CI = –9.850 ~ –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 | | | Percentiles | | N | | | Percentiles | | |
	Valid	Missing	Median	Q1	Q3	Valid	Missing	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	23	0	149.5	72	212	32	0	210.4	86.92	246.25	0.147
IL-6 levels on admission	10	13	8.85	4.45	22.85	20	12	42.25	11.25	95.52	0.015
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 | Series | Not treated with urinary trypsin inhibitor therapy | | | Treated with urinary trypsin inhibitor therapy | | | |
		N	(%)	Missing data N (%)	N	%	Missing data N (%)	p value
Gender	Male	18	78.3	0	28	87.5	0	0.46
	Female	5	21.7		4	12.54		
Severity of disease at admission	Mild	8	34.8	0	10	31.3		0.517
	Moderate	14	60.9		19	59.4	2 (3.6%)	
	Severe	1	4.3		1	3.1		
Charlson's Co-morbidity index	0	2	8.7	0	4	12.5		0.158
	1	6	26.1		7	21.9		
	2	7	30.4		4	12.5		
	3	5	21.7		6	18.8		
	4	1	4.3		9	28.1	0	
	5	0	0		1	3.1		
	6	2	8.7		1	3.1		
	7							
Anti-viral therapy		19	82.6	0	31	96.9	0	0.149
Anticoagulation therapy		22	95.7	1 (4.3%)	30	93.8	0	0.141
Corticosteroid therapy		23	100	0	32	100	0	NA
IL-6 inhibitor therapy (toclizumab)								
Oxygen therapy		22	95.7	0	31	96.9	1	1
ICU stay		14	60.9	0	19	59.4	0	0.91
Ventilation support		4	17.4	0	4	12.5	0	0.7
Mode of ventilation support	None	17	73.9	2 (8.7)	22	68.8	6 (18.8)	0.25
	Non-invasive	1	4.3		0	0		
	Invasive	3	13		4	12.5		

Final in hospital Outcome	Survived	19	82.6	0	29	90.6	0	**0.435**
	Deceased	4	17.4		3	9.4		

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	0.099	2.446	**0.435**
ICU length of stay	1.242	1.164	1.324	<0.000	1.073	0.927	1.241	**0.28**

ARI, 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
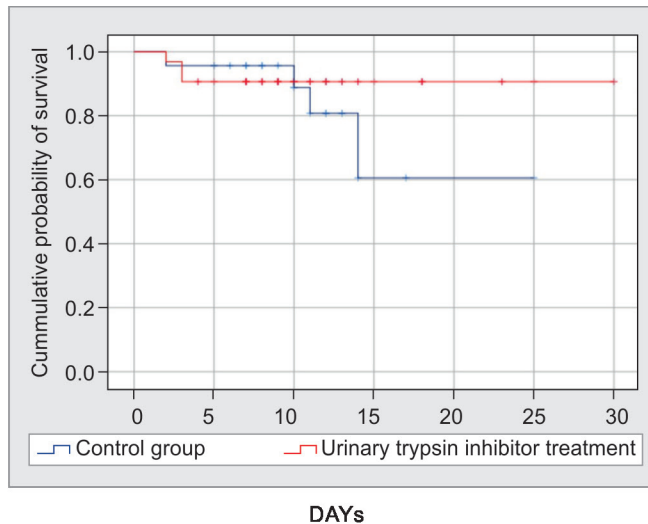
Means for Survival Time				
		Mean		
Urinary trypsin inhibitor treatment			95% Confidence interval	
	Estimate	Std. Error	Lower bound	Upper bound
No	19.624	2.368	14.983	24.266
Yes	27.438	1.409	24.677	30.198
Overall	25.440	1.691	22.126	28.755
Overall comparisons				
	Chi-square	df		p-value
Log rank (Mantel-Cox)	0.668	1		0.414

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

p-value 0.024; TNF-α: SMD=−5.666, 95% CI=−11.083 ~ −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 ~ 0.61), the occurrence of ventilator-associated pneumonia rate (RR=0.50, 95% CI: 0.36 ~ 0.69), and shortening duration of mechanical ventilation (SMD=−1.29, 95% CI: −1.76 ~ −0.83), length of ICU stay (SMD=−1.38,

95% CI: −1.95 ~ −0.80), and hospital stay (SMD =−1.70, 95% CI:−2.63 ~ −0.77), and ulinastatin significantly improved oxygenation index, respiratory rate, and serum inflammatory factors (TNF-α, IL-1β, IL-6, IL-8).[12] 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

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 anticoagulation, 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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