LETTER

Camostat mesylate therapy in critically ill patients with COVID-19 pneumonia

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Dear Editor,

Camostat mesylate inhibits several serine proteases implicated in SARSCoV and SARS-CoV-2 virus-to-host cell membrane fusion, such as transmembrane serine protease (TMPRSS) 2, − 13, and − 11D/E/F [1–3]. In particular, inhibition of the SARS-CoV-2-activating host cell TMPRSS2 have been shown to block SARS-CoV-2 entry into the lung cells and represents, therefore, a possible therapeutic option in patients with coronavirus disease 2019 (COVID-19) [4]. A preliminary observation suggested that camostat mesylate may be also effective to treat the most advanced cases of COVID-19 with organ dysfunction [5]; however, randomized clinical trials are ongoing.

In a retrospective analysis of 371 adult patients (>18 years) admitted to the intensive care unit (ICU) of Al Ain Hospital, Abu Dhabi, United Arabs Emirates between March 16 and July 19, 2020 with COVID-19 pneumonia, we assessed whether treatment with camostat mesylate is associated with an improved outcome (Figure S1–2, Supplementary material). Details of data collection, patients' management, and statistical methods are presented in appendix S1 of the supplementary material. Off-label camostat mesylate (Foipan®, Osaka, Japan) was given to 141 (38%) patients on admission to the ICU (200 mg po TID) for 7 days (Table 1 and table S1–2 of the Supplementary material). The overall ICU and hospital

lengths of stay were 9 (25–75% interquartile range 5–17) and 18 (25–75% interquartile range 13–29) days, respectively, and ICU and hospital mortality rates were both 20.2% ($n = 75$). ICU/hospital mortality rate were lower (9.9 vs. 26.5, $p < 0.001$); whereas, the hospital length of stay was longer in patients who received camostat mesylate than who did not (Table 1).

In a propensity score-adjusted multivariable Cox proportional hazard analysis in the whole cohort, camostat mesylate therapy was independently associated with a lower risk of in-hospital death, right censored at 60 days (relative hazard 0.31, 95% confidence interval 0.15–0.60, $p = 0.001$; table S3 and figure S3 of the supplementary material). Moreover, after inversed propensity treatment weight (IPTW)-adjustment and robust estimation using generalized estimating equations, camostat mesylate therapy was found to be independently associated with a lower risk of in-hospital death (odds ratio 0.254; 95% confidence interval 0.108–0.595, $p < 0.001$). In 122 propensity score-matched patients (61 pairs), ICU/hospital mortality rates (9.8 vs. 29.5, $p = 0.006$), the need for vasopressor therapy (45.9 vs. 67.2%, $p = 0.018$) or invasive mechanical ventilation (47.5 vs. 67.2%, $p = 0.045$) during the ICU stay were lower; whereas, 60-day survival was higher (log rank $Chi^2 = 18.6$, $p < 0.001$) in patients treated with camostat mesylate than those who were not (Table 1, tables S1–3 and figure S4 of the supplementary material). Nonetheless, despite of the observed therapeutic benefit of camostat mesylate in these patients, our analysis may be limited by the specific case-mix, the residual confounding effect due to unmeasured variables, and the influence of concomitant therapies.

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In summary: in this cohort, a therapeutic benefit of camostat mesylate therapy was observed in critically ill patients with COVID-19 pneumonia using several propensity score-based statistical techniques. Randomized control trials should identify target populations for this promising therapy throughout COVID-19 disease trajectory.

Table 1 Characteristics of the study groups on admission to the ICU

	The whole cohort (n = 371)			Propensity score-matched cohort (n = 122)		
	Camostat	No camostat	*p* value	Camostat	No camostat	*p* value
N	141	230		61	61	
Age, years, mean ± SD	53 ± 13	53 ± 14	0.672	52 ± 12	55 ± 14	0.140
Gender, male (%)	119 (84.4)	195 (84.8)	0.920	55 (90.2)	48 (78.7)	0.081
BMI, kg/m², mean ± SD	31.4 ± 21.7	31.5 ± 24.4	0.374	33.5 ± 31.9	33.1 ± 22.3	0.684
Referring facility, n (%)			0.032			0.866
Other hospital, same city	76 (53.9)	91 (39.6)		31 (50.8)	30 (49.2)	
Primary admission	47 (33.3)	102 (44.3)		23 (37.7)	24 (39.3)	
Hospital ward[a]	11 (7.8)	19 (8.3)		5 (8.2)	5 (8.2)	
Other hospital, another city	7 (5)	18 (7.8)		2 (2.3)	2 (3.3)	
Ethnicity, n (%)			0.087			0.652
South Asian	81 (57.4)	150 (65.2)		34 (55.7)	33 (54.1)	
Arab	51 (36.2)	65 (28.3)		22 (36.1)	24 (39.3)	
Asian, others	7 (5)	12 (5.2)		3 (4.9)	3 (4.9)	
Other	2 (1.4)	3 (1.3)		2 (3.3)	1 (1.6)	
APACHE II score, mean ± SD	11 ± 7	11 ± 9	0.795	11 ± 8	12 ± 10	0.454
Comorbid conditions, n (%)						
Diabetes mellitus	66 (46.8)	98 (42.6)	0.429	30 (49.2)	31 (50.8)	0.856
Systemic hypertension	70 (49.6)	90 (39.1)	0.047	28 (45.9)	29 (47.5)	0.856
Cardiovascular disease, any	27 (19.1)	36 (15.7)	0.384	8 (13.1)	12 (19.7)	0.328
Ischemic heart disease	17 (12.1)	23 (10)	0.535	4 (6.6)	8 (13.1)	0.224
Congestive heart failure	6 (4.3)	6 (2.6)	0.384	2 (3.3)	1 (1.6)	1.000
Atrial fibrillation/flutter	2 (1.4)	5 (2.2)	0.714	1 (1.6)	3 (4.9)	0.619
Valvular heart disease	–	2 (0.9)	0.528	–	–	–
Peripheral vascular disease	1 (0.7)	–	0.380	–	–	–
Chronic renal disease, any	17 (12.1)	33 (14.3)	0.530	6 (9.8)	8 (13.1)	0.570
End stage renal disease	4 (2.8)	3 (1.3)	0.434	3 (4.9)	–	0.244
Comorbidities, n			0.180			0.549
None	49 (34.8)	96 (41.7)		25 (41)	20 (32.8)	
1	35 (24.8)	56 (24.3)		11 (18)	17 (27.9)	
2	33 (23.4)	42 (18.3)		16 (26.2)	13 (21.3)	
3	17 (12.1)	27 (11.7)		7 (11.5)	7 (11.5)	
≥ 4	7 (4.9)	9 (3.9)		2 (3.3)	4 (6.6)	
Procedures on admission to the ICU, n (%)						
Invasive mechanical ventilation	13 (9.2)	41 (17.8)	< 0.001	9 (14.8)	10 (16.4)	0.803
Renal replacement therapy	6 (4.3)	15 (6.5)	0.489	4 (6.6)	2 (3.3)	0.680
ICU/hospital mortality, n (%)	14 (9.9)	61 (26.5)	< 0.001	6 (9.8)	18 (29.5)	0.006
ICU LOS, median (IQR)	10 (6–23)	9 (5–16)	0.069	11 (6–28)	11 (6–28)	0.864
Hospital LOS, median (IQR)	19 (13–32)	17 (11–25)	0.011	21 (14–37)	18 (12–41)	0.351

APACHE II acute physiologic and chronic health evaluation score, *BMI* body mass index, *ICU* intensive care unit, *IQR* 25–75% interquartile range, *LOS* length of stay, *SD* standard deviation

Missing values (whole cohort: camostat/no camostat: weight: 3 (2/1), BMI: 3 (2/1), APACHE II: 10 (9/1)

[a] 30 patients were referred from the hospital ward to the ICU after a range of 3–9 days; 11 have received camostat mesylate (prehospital stay; range 3–7 days) and 19 patients did not (prehospital stay; range 3–9 days)

Supplementary Information

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Authors contribution
KI, YS, AT, MB, and HB designed the scientific work. YS, HB, GB, AT, D Munde, D Monk, SB, and KMA contributed to data collection and handling. YS, SB, HB performed the statistical analysis. AT, KI, KMA, D Munde, and SB reviewed the literature. YS, KI, AT, GB, MB, and SB wrote the first draft of the manuscript. All the authors reviewed, revised, and approved the submitted manuscript. KI and HB have complete access to the clinical data of the reported cases and hold responsibility for integrity and correctness of data.

Availability of data and material
The datasets analyzed in the current manuscript are available from the corresponding author on reasonable request.

Code availability
The software codes are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest
The authors declare that they do not have conflict of interests in relation to this manuscript.

Ethics approval and consent to participate
The off-label use of camostat mesylate was recommended by the Department of Health, Abu Dhabi (PO box 5674, Abu Dhabi, UAE). Informed consents for the off-label use of camostat mesylate were obtained on admission to the hospital according to the guidelines of UAE-Ministry of health. The analysis provided in the current manuscript was done retrospectively after obtaining the approval of the responsible institutional review board (Institutional review board of Department of Health, Abu Dhabi, PO box 5674, Abu Dhabi, UAE, application number: DOH/CVDC/2020/1669, August 8th 2020), which waived informed consent for data collection and analysis due to the retrospective nature of data collection.

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