

Camostat Mesylate May Reduce Severity of Coronavirus Disease 2019 Sepsis: A First Observation

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Objectives: Severe acute respiratory syndrome coronavirus 2 cell entry depends on angiotensin-converting enzyme 2 and transmembrane serine protease 2 and is blocked in cell culture by camostat mesylate, a clinically proven protease inhibitor. Whether camostat mesylate is able to lower disease burden in coronavirus disease 2019 sepsis is currently unknown.

Design: Retrospective observational case series.

Setting: Patient treated in ICU of University hospital Göttingen, Germany.

Patients: Eleven critical ill coronavirus disease 2019 patients with organ failure were treated in ICU.

Interventions: Compassionate use of camostat mesylate (six patients, camostat group) or hydroxychloroquine (five patients, hydroxychloroquine group).

Measurements and Main Results: Clinical courses were assessed by Sepsis-related Organ Failure Assessment score at days 1, 3, and 8. Further, viral load, oxygenation, and inflammatory markers were determined. Sepsis-related Organ Failure Assessment score was comparable between camostat and hydroxychloroquine groups upon ICU admission. During observation, the Sepsis-related Organ Failure

Assessment score decreased in the camostat group but remained elevated in the hydroxychloroquine group. The decline in disease severity in camostat mesylate treated patients was paralleled by a decline in inflammatory markers and improvement of oxygenation.

Conclusions: The severity of coronavirus disease 2019 decreased upon camostat mesylate treatment within a period of 8 days and a similar effect was not observed in patients receiving hydroxychloroquine. Camostat mesylate thus warrants further evaluation within randomized clinical trials.

Key Words: camostat mesylate; coronavirus disease 2019; sepsis; Sepsis-related Organ Failure Assessment

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19) (1). Antiviral interventions against SARS-CoV-2 are urgently needed and the fastest way to obtain antivirals might be to repurpose drugs developed for treatment of diseases unrelated to COVID-19. The serine protease inhibitor camostat mesylate, which is approved for treatment of pancreatitis and reflux disease in Japan, inhibits the SARS-CoV-2-activating host cell protease transmembrane serine protease 2 (TMPRSS2) and thereby blocks SARS-CoV-2 infection of cultured lung cells (2). However, it is unknown whether camostat mesylate is safe and effective when used for treatment of COVID-19. In this small retrospective case series, we compare clinical ICU courses of patients with severe COVID-19 who received camostat mesylate or were treated with hydroxychloroquine.

MATERIALS AND METHODS

The first 11 COVID-19 patients treated in the ICU of the Department of Anesthesiology at Göttingen University Medical Centre from March 2020 to May 2020 were included in this case series. We retrospectively explored the possible impact of supportive therapy plus antiviral treatment in critically ill COVID-19 patients. The supportive therapy and our standard operating procedure (SOP) for

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SARS-CoV-2 related sepsis was approved by our internal clinical committee by the end of February 2020 and focused on organ support according to current sepsis and acute respiratory distress syndrome

(ARDS) guidelines and was not modified during the observation. Briefly, our COVID-19 SOP included x-ray and recruitment CT scan when possible to better adjust our ICU ventilator strategy. A

TABLE 1. Comparison Between Camostat Mesylate and Non-Camostat Mesylate Treated Coronavirus Disease 2019 Patients

Parameter	Camostat Group (n = 6)	Hydroxychloroquine Group (n = 5)
Demographic		
Age (yr)	71 (59–76)	66 (45–75)
Sex (man/woman)	4/2	4/1
Arterial hypertension (n)	4	4
Obesity (n)	3	2
Hyperlipoproteinemia (n)	2	1
Diabetes mellitus (n)	2	1
Smoking history (n)	1	2
COVID-19 course		
Days of symptoms	5 (2–8)	6 (3–10)
Fever (n)	1	1
Cough (n)	2	1
Dyspnea (n)	6	5
ICU score day 1		
SAPS II	45 (35–71)	44 (38–64)
Predicted SAPS II mortality (%)	36 (17–85)	33 (21–78)
Parameters upon ICU admission		
Heart rate (1/min)	98 (57–149)	110 (78–123)
Respiratory rate (systolic blood pressure) (mm Hg)	96 (57–158)	108 (56–160)
Temperature (°C)	38.7 (36.1–39.0)	38.1 (37.4–38.5)
ICU data		
Mechanical ventilation (n)	6	5
Pressure support ventilation	2	3
Controlled ventilation	4	2
Extracorporeal membrane oxygenation (n)	1	0
Length of stay ICU (d)	14 (4–24)	36 (11–55)
Renal replacement, first 24 hr	1	1
Death related to COVID-19 (n)	1	2
Oxygenation (PaO ₂ /FiO ₂) ^a		
Day 1	159 (85–404)	132 (67–202)
Day 3	160 (98–275)	136 (81–228)
Day 8	240 (82–313)	120 (69–269)

(Continued)

TABLE 1. (Continued). Comparison Between Camostat Mesylate and Non-Camostat Mesylate Treated Coronavirus Disease 2019 Patients

Parameter	Camostat Group (n = 6)	Hydroxychloroquine Group (n = 5)
Viral load (gene equivalent per reaction)		
Day 1	725 (62.2–1.04 × 10 ⁶)	35 (26–16.5 × 10 ⁶)
Day 3	146 (0.01–0.83 × 10 ⁶)	328 (0.01–1.1 × 10 ⁶)
Day 8	197 (0.01–2,970)	18 (0.01–544)
Leucocytes (10 ³ /μL)		
Day 1	8.1 (3.2–19.4)	7.9 (6.5–13.2)
Day 3	9.8 (4.5–15.0)	12.7 (5.8–18.9)
Day 8	11.0 (8.5–16.8)	16.0 (8.1–17.1)
Lymphocytes (% of leucocytes)		
Day 1	8.8 (5.7–34.8)	8.6 (4.4–9.5)
Day 3	7.9 (6.6–33.8)	8.7 (3.9–10.5)
Day 8	13.5 (11.9–16.3)	7.81 (4.7–11.6)
D-dimer (mg/L)		
Day 1	2.63 (0.93–5.54)	0.8 (0.44–3.57)
Day 3	1.51 (0.47–3.79)	2.1 (0.96–24.41)
Day 8	1.91 (0.30–12.6)	3.19 (0.9–6.9)
Ferritin (μg/L)		
Day 1	1,229 (514–2,653)	1,552 (368–5,947)
Day 3	2,345 (2,345–2,345)	1,214 (732–5,860)
Day 8	328 (90–566)	1,203 (796–1,610)
C-reactive protein (mg/L)		
Day 1	165.0 (33.7–263.2)	98.0 (11.3–105.4)
Day 3	190.3 (81.6–254.0)	105.7 (11.3–265.8)
Day 8	37.1 (17.7–411.0)	165.2 (85.3–245.1)
Procalcitonin (μg/L)		
Day 1	1.04 (0.22–1.60)	0.51 (0.11–1.03)
Day 3	1.63 (0.89–2.38)	0.69 (0.10–1.26)
Day 8	0.28 (0.04–0.46)	0.58 (0.25–6.24)
Interleukin-6 (pg/mL)		
Day 1	112.3 (90.2–141.6)	66.9 (31.1–348.2)
Day 3	84.3 (59.1–109.6)	82.0 (50.1–102.8)
Day 8	34.7 (13.6–164.3)	109.8 (89.3–130.4)

COVID-19 = coronavirus disease 2019, SAPS II = Simplified Acute Physiology Score II.

*Excluding extracorporeal membrane oxygenation patient.

Data are presents as absolute numbers or as median and range.

functional test for the oxygenation capacity was performed upon ICU admission and once daily (FiO₂ 100% for 5 min). The ventilator strategy was based on our ARDS protocol and included low tidal volume (6 mL/kg ideal body weight) with tolerable permissive hypercapnia.

Physiologic accepted targets were Pao₂ of 60 mm Hg, oxygen saturation of greater than 90%, and pH 7.2. A transesophageal catheter was used to measure transpulmonary pressure to adjust positive end-expiratory pressure. Prone position for 16 hours was eventually tried

to improve gas exchange when ventilation/perfusion mismatch was no longer acceptable and CT scans showed recruitable lung areas. We early established a continuous hemodynamic monitoring to minimize volume overload and examined possible and reversible reasons for compromised gas exchange, such as atelectasis or pleural effusion by x-ray or ultrasound daily.

Our local ethics board at the University Medical Center of Göttingen approved inclusion of all ICU patients in an ongoing sepsis observational trial (reference 25/4/19Ü). Patients were treated within the context of compassionate use. Our local ethics board was contacted and approval for compassionate use was waived in view of the retrospective nature of the analysis. All COVID-19 patients received antiviral treatments not specified or approved for SARS-CoV-2 infection after written informed consent about emergency; compassionate use was obtained from relatives or their legal representatives. Antiviral treatment was first applied when patients were transferred to university ICU. In the early phase of the pandemic in Germany, antiviral treatment was exclusively reserved for tertiary center ICUs. Hydroxychloroquine was at the disposal for ICU intensivists at any time because this drug is in stock for chronic disease such as patients with systemic lupus erythematosus. When doubts were raised regarding effectiveness of hydroxychloroquine, this antiviral strategy was replaced by administration of camostat mesylate by mid of March (3, 4). The following doses were used: hydroxychloroquine was administered with a loading dose of 400 mg on day 1 followed by 200 mg days 2–5 and camostat mesylate at the maximum dose of 3×200 mg daily for 5 days according to information based on a protocol of a larger trial in Denmark (clinical trials reference: NCT04321096). No patient received steroids or other anti-inflammatory treatments such as tocilizumab.

We chose to show ICU clinical course, vital signs, and laboratory measures taken on day of admission (day 1) and days 3 and 8. Simplified Acute Physiology Score II (SAPS II) and Sepsis-related Organ Failure Assessment (SOFA) were chosen as surrogate marker of disease severity, and the SOFA was our primary outcome variable.

RESULTS

All patients had been diagnosed with COVID-19 on the day of their hospital admission by detection of SARS-CoV-2 RNA in nasopharyngeal/oropharyngeal swabs by quantitative reverse transcription polymerase chain reaction (5). All patients were infected with SARS-CoV-2 in hot spot areas and presented with typical COVID-19 symptoms upon hospital admission (Table 1). After a symptomatic period of 2–10 days, patients were transferred to ICU for further treatment (Table 1). Five patients (45–75 yr, one woman) received hydroxychloroquine and six patients (59–76 yr, two women) were treated with camostat mesylate between days 1 and 5. All patients had preexisting medical conditions, most frequently arterial hypertension followed by obesity (Table 1). The clinical status of disease assessed by SAPS II was 45 in the camostat and 44 in the hydroxychloroquine group with a comparable predicted mortality of 33–36% in both groups (Table 1). In all camostat mesylate treated patients, a decrease of pro-inflammatory cytokines (interleukin [IL]-6) and other inflammatory markers (ferritin, C-reactive protein [CRP], procalcitonin, and D-dimer) was observed along with improvement of the oxygenation index at day 8. Overall the decrease of inflammatory markers was paralleled by a rapid improvement of organ failure assessed by SOFA score. In camostat mesylate treated patients, the median SOFA score decreased within 8 days from 9 to 4 points (Fig. 1). One out of six patients died and median hospitalization was 14 days. The five patients in the hydroxychloroquine group showed a prolonged systemic inflammation regarding levels of inflammatory markers such as IL-6, ferritin, CRP, and procalcitonin (Table 1). The oxygenation index remained low (Table 1). Overall the disease severity was not rapidly improving, and consequently, the median SOFA score remained high (9 points). Two patients died and hospitalization of hydroxychloroquine treated patients was prolonged (median ICU stay, 36 d). In sum, camostat mesylate but not hydroxychloroquine treatment was associated with improvement of inflammatory markers and clinical severity from COVID-19.

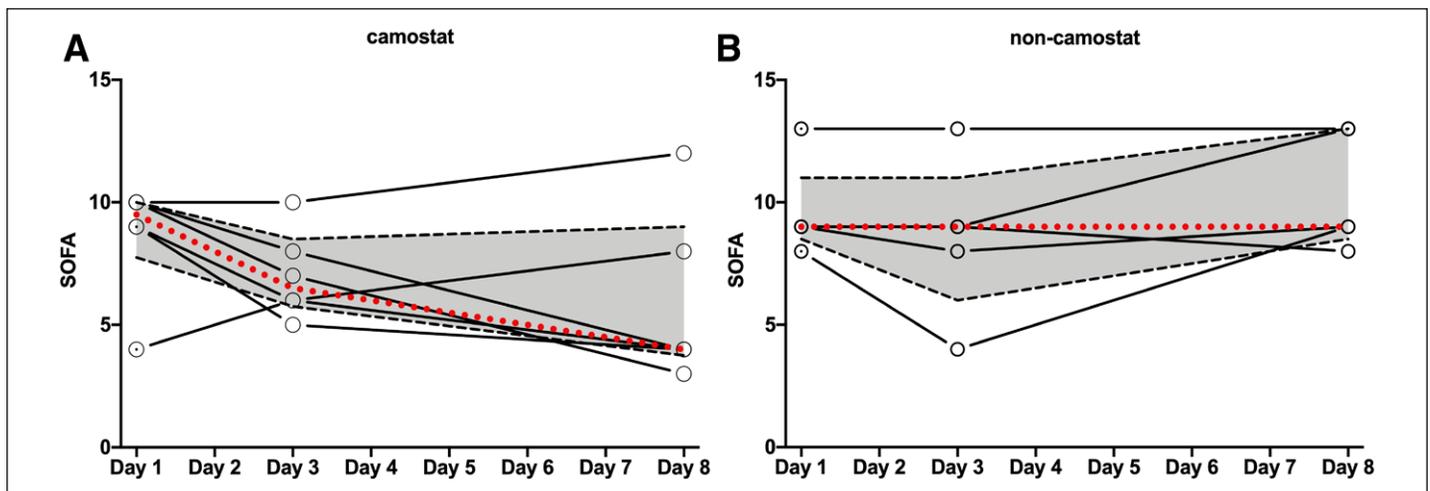


Figure 1. Intensive care clinical courses of COVID-19 patients treated with camostat mesylate and hydroxychloroquine expressed as severity of sepsis. Impact of camostat mesylate (A) and hydroxychloroquine treatment (B) on organ failure in critical ill coronavirus disease 2019 patients assessed by Sepsis-related Organ Failure Assessment (SOFA) score. Gray bars indicate first quartile and third quartile, the dotted line median SOFA of six patients treated with camostat mesylate, and five patients treated with hydroxychloroquine. Solid lines indicate the individual course of disease severity.

DISCUSSION

We compared the clinical course in critically ill COVID-19 patients treated either with camostat mesylate or hydroxychloroquine. It should be noted that recent evidence indicates that hydroxychloroquine does not block SARS-CoV-2 infection of lung cells or protect against COVID-19 (6–8). The absence of beneficial effects associated with hydroxychloroquine treatment was, thus, retrospectively, not unexpected. In contrast, patients treated with camostat mesylate showed a decrease in disease severity assessed by the SOFA score. The SOFA score includes sepsis defining parameters, suggesting that camostat mesylate may reduce virus spread from the lung to other organs and/or may dampen the inflammatory response. Extrapulmonary spread of SARS-CoV-2 was not examined in the present study and viral load in nasopharyngeal swabs was variable and not correlated with organ complications (Table 1). Overall, levels of CRP, ferritin, procalcitonin, and IL-6 decreased in camostat mesylate treated patients while only ferritin decreased in patients receiving hydroxychloroquine (Table 1). Interestingly, in two patients in the camostat mesylate treated group with increasing SOFA scores, CRP levels did not fall, respectively, rise within 8 days, and IL-6 increased in one patient. In this context, it is noteworthy that camostat mesylate reduces release of tumor necrosis factor- α and monocyte chemoattractant protein-1 (MCP-1) from lipopolysaccharide treated rat monocytes in cell culture and reduces the expression of MCP-1, transforming growth factor-beta, platelet-derived growth factor, IL-1b, and IL-6 in the pancreas in a rat model for pancreatitis (9). Furthermore, in a murine model of pulmonary fibrosis camostat mesylate protected against lung injury (10). Finally, TMPRSS2 knockout mice not only showed reduced coronavirus spread but also diminished immunopathology and reduced expression of inflammatory chemokine and/or cytokines upon intranasal stimulation with polyinosinic:polycytidylic acid (11). It is thus conceivable that camostat mesylate may not only impede viral spread but may ameliorate uncontrolled cytokine release in COVID-19 patients. Randomized controlled studies in COVID-19 patients with camostat mesylate are currently ongoing (<https://www.sciencemag.org/news/2020/04/these-drugs-don-t-target-coronavirus-they-target-us>) and could address this possibility (12).

The small group sizes and the retrospective observational nature strongly limit representativeness of the results and individual patient-related factors such as comorbidities may have biased the results even if risk profiles between camostat mesylate and hydroxychloroquine treated patients were comparable (Table 1). The reduction of inflammatory markers might reflect natural resolution of the infection and not necessarily of antiviral treatment. Nonetheless, despite the small number of cases investigated here, it is remarkable that the degree of organ failure was equal at ICU admission in both groups, suggesting that camostat mesylate may have contributed to the positive course of COVID-19 sepsis.

CONCLUSIONS

These findings, jointly with the described antiviral activity of camostat mesylate in cell culture (2, 7) and rodents (13), and

its potential immune-modulatory properties combined with its safety as an approved drug for pancreatitis in Japan, indicate that systematic exploration of camostat mesylate for COVID-19 treatment is warranted.

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REFERENCES

- Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team: A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382:727–733
- Hoffmann M, Kleine-Weber H, Schroeder S, et al: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181:271–280.e8
- Das S, Bhowmick S, Tiwari S, et al: An updated systematic review of the therapeutic role of hydroxychloroquine in coronavirus disease-19 (COVID-19). *Clin Drug Investig* 2020; 40:591–601
- Wu R, Wang L, Kuo HD, et al: An update on current therapeutic drugs treating COVID-19. *Curr Pharmacol Rep* 2020 May 11:1–15. doi: 10.1007/s40495-020-00216-7 [Epub ahead of print]
- Corman VM, Landt O, Kaiser M, et al: Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill* 2020; 25:2000045
- Cavalcanti AB, Zampieri FG, Rosa RG, et al: Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *New Engl J Med* 2020 Jul 23. [online ahead of print]
- Hoffmann M, Mösbauer K, Hofmann-Winkler H, et al: Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. *Nature* 2020; 585:588–590
- Maisonasse P, Guedj J, Contreras V, et al: Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature* 2020; 585:584–587
- Gibo J, Ito T, Kawabe K, et al: Camostat mesilate attenuates pancreatic fibrosis via inhibition of monocytes and pancreatic stellate cells activity. *Lab Invest* 2005; 85:75–89
- Bardou O, Menou A, François C, et al: Membrane-anchored serine protease matriptase is a trigger of pulmonary fibrogenesis. *Am J Respir Crit Care Med* 2016; 193:847–860
- Iwata-Yoshikawa N, Okamura T, Shimizu Y, et al: TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *J Virol* 2019; 93:e01815–e01818
- Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al: Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 2020; 383:590–592
- Zhou Y, Vedantham P, Lu K, et al: Protease inhibitors targeting coronavirus and filovirus entry. *Antiviral Res* 2015; 116:76–84