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Research paper

Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial.

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A R T I C L E   I N F O

A B S T R A C T

Background: The trans-membrane protease serine 2 (TMPRSS2) is essential for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cell entry and infection. Efficacy and safety of TMPRSS2 inhibitors in patients with coronavirus disease 2019 (Covid-19) have not been evaluated in randomized trials.

Methods: We conducted an investigator-initiated, double-blind, randomized, placebo-controlled multicenter trial in patients hospitalized with confirmed SARS-CoV-2 infection from April 4, to December 31, 2020. Within 48 h of admission, participants were randomly assigned in a 2:1 ratio to receive the TMPRSS2 inhibitor camostat mesilate 200 mg three times daily for 5 days or placebo. The primary outcome was time to discharge or clinical improvement measured as ≥ 2 points improvement on a 7-point ordinal scale. Other outcomes included 30-day mortality, safety and change in oropharyngeal viral load.

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Findings: 137 patients were assigned to receive camostat mesilate and 68 to placebo. Median time to clinical improvement was 5 days (interquartile range [IQR], 3 to 7) in the camostat group and 5 days (IQR, 2 to 10) in the placebo group (*P* = 0·31). The hazard ratio for 30-day mortality in the camostat compared with the placebo group was 0·82 (95% confidence interval [CI], 0·24 to 2·79; *P* = 0·75). The frequency of adverse events was similar in the two groups. Median change in viral load from baseline to day 5 in the camostat group was -0·22 $\log_{10}$ copies/mL (*p* <0·05) and -0·82 $\log_{10}$ in the placebo group (*P* <0·05).

Interpretation: Under this protocol, camostat mesilate treatment was not associated with increased adverse events during hospitalization for Covid-19 and did not affect time to clinical improvement, progression to ICU admission or mortality. ClinicalTrials.gov Identifier: NCT04321096. EudraCT Number: 2020-001200-42.

Research in context

Evidence before this study

We searched PubMed on 4 February 2021, for studies using combination of the terms "Camostat Mesilate/Mesylate" OR "TMPRSS2 inhibition"; AND "Covid", "Covid-19″, "coronavirus" OR "SARS-CoV-2″. We did not restrict our search by date or language. Blocking host receptors and enzymes involved in SARS-CoV-2 replication has been highlighted as a potential novel treatment strategy. At cellular level, the trans-membrane protease serine 2 (TMPRSS2) primes the spike protein of human coronaviruses and facilitates cell entry and infection. Camostat mesilate is an inhibitor of TMPRSS2 and has been shown to be a potent antiviral agent against SARS-CoV-2 *in vitro* and against SARS-CoV-1 *in vivo (mice)*. Based on the promising preclinical findings, camostat mesilate and other TMPRSS2 inhibitors are being used off-label in the treatment of Covid-19 around the world. This off-label use has been further fueled by case reports that have indicated that a beneficial effect of TMPRSS2 inhibitors in the treatment of Covid-19.

Added value of this study

The hypothesis underlying our trial was that TMPRSS2 inhibition would block SARS-CoV-2 replication in infected patients leading to reduced viral loads, and that this in turn would lower the risk of hyper-inflammation and prevent disease progression. However, the results from our double-blind randomized placebo-controlled trial show that among patients hospitalized with Covid-19 camostat mesilate treatment did not significantly improve time to clinical improvement, the risk of intubation or death, time to discontinuation of supplemental oxygen, or any other efficacy outcomes.

Implications of all the available evidence

Our findings show that 200 mg t.i.d. camostat mesilate is not an effective treatment for hospitalized patients with Covid-19. However, we cannot exclude the possibility that camostat mesilate or other TMPRSS2 inhibitors administered in higher doses or during the very early phase of Covid-19 might be effective in lowering the risk of disease progression.

1. Introduction

Coronavirus disease 2019 (Covid-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel pandemic coronavirus first identified in December 2019 [1−3]. By February 2021, there have been more than 100 million confirmed Covid-19 cases and more than 2.3 million deaths have been attributed to Covid-19 [4].

After a pre-symptomatic incubation period, the acute viral phase in patients with symptomatic Covid-19 usually presents as influenza-like symptoms [5]. In most persons, these symptoms resolve spontaneously within days or weeks but in some individuals, the illness progresses to hypoxemic respiratory failure [6]. Studies suggest that disease progression to respiratory failure is associated with a hyper-inflammatory response [7,8].

Numerous therapeutic agents have been tested against Covid-19 [9−11]. In the early disease phase, blocking viral replication might lead to faster recovery and reduced disease severity. This is the mechanism of action of remdesivir which was shown to lead to faster recovery in hospitalized Covid-19 patients [12]. Among outpatients, early administration of monoclonal SARS-CoV-2 specific antibodies lead to reduced risk of disease progression [13]. Anti-inflammatory drugs such as dexamethasone, which significantly decreases mortality among hospitalized Covid-19 patients, are important for reducing cytokine levels and immune-mediated pathogenesis in the hyper-inflammatory phase [14]. However, considering the modest clinical benefit of remdesivir, there is a urgent need for better antiviral therapeutic options for COVID-19.

Blocking host receptors and enzymes involved in SARS-CoV-2 replication has been highlighted as a potential novel treatment strategy [15,16]. At cellular level, the trans-membrane protease serine 2 (TMPRSS2) primes the spike protein of human coronaviruses and facilitates cell entry and infection [17,18]. Camostat mesilate is an inhibitor of TMPRSS2 and has been shown to be a potent antiviral agent against SARS-CoV-2 *in vitro* and against SARS-CoV-1 *in vivo* [17,19,20]. Camostat mesilate was originally developed in 1980s in Japan and it is licensed for the treatment of chronic pancreatitis and postoperative reflux esophagitis [21]. However, the optimal dosing of Camostat mesilate in the treatment of COVID-19 is unknown. In cell cultures, Camostat mesilate reduced SARS−CoV−2 cell entry by 50% (EC_{50}) at a concentration to 1 μM and 90% at 5 μM (EC_{90}) [17]. In viral challenge experiments with SARS−CoV-1 in mice, camostat mesilate dosed at 30 mg/kg two times daily reduced mortality by 60%. [19] If the dose used in mice is translated on the basis of body surface area, the equivalent dosing in a 70−kg human would be 170 mg × 2 daily [22]. Encouragingly, a recent case-series on COVID-19 patients admitted to the intensive care unit indicated a clinical benefit of camostat mesilate dosed at 200 mg three times daily in reducing the organ failure score [23]. Another clinically approved TMPRSS2 inhibitor, nafamostat, has also shown effect *in vitro*, but requires intravenous dosing. Nafamostat has not been tested in animal models against neither SARS-CoV-1 or −2 [17,18].

We conducted an investigator-initiated trial in patients hospitalized with Covid-19 to evaluate the clinical efficacy and safety of camostat mesilate.

2. Methods

2.1. Trial design

This phase IIa double-blind, randomized, placebo-controlled, multicenter trial enrolled adults hospitalized with Covid-19. Inclusion

criteria were symptomatic Covid-19 infection defined as PCR-positive for SARS-CoV-2 in respiratory tract samples and hospital admission for ≤ 48 h. Patients unable to understand or sign the informed consent form (*e.g.* those requiring invasive mechanical ventilation at study entry) were not eligible. Exclusion criteria included baseline values of serum total bilirubin ≥ 3 upper limit of normal range and estimated glomerular filtration rate (eGFR) ≤ 30 mL/min, pregnancy or breastfeeding (full list of entry criteria is provided in the protocol, Appendix 1).

2.2. Randomization and masking

The trial was conducted at eight Danish sites (Aalborg, Aarhus, Herning, Hillerod, Hjorring, Odense, Randers and Viborg) and one in Sweden (Örebro). Participants were enrolled at the clinical department in the trial sites and randomly assigned in a 2:1 ratio to receive either camostat mesilate or placebo. Two tablets 100 mg camostat mesilate or two placebo tablets similar in size and color were administered orally three times daily (every 8 h) for five days. The daily dosing of camostat mesilate was based on the approved dosing for its primary indication in Japan [21]. Placebo tablets were provided by the pharmacy at Aarhus University Hospital to Danish sites and by STMpharmaPRO, Italy to the Swedish site, and delivered to trial sites in sealed blinded packages. The trial was conducted in accordance with Good Clinical Practice and reported in accordance with the CONSORT 2010 statement. The protocol was approved by the Danish Medicines Agency and Swedish Medical Product Agency (both #2020−001,200−42), and the National Committee on Health Research Ethics in Denmark (#1−10−72−77−20) and Sweden (#2020−02,093). An independent safety monitoring committee regularly monitored unblinded data to ensure trial participants safety.

Patients requiring hospitalization for Covid-19 were screened and enrolled within 48 h of admission. A written informed consent was obtained from each participant prior to any trial-related procedures. Trial data were collected by trial PIs and managed using Research Electronic Data Capture (REDCap) hosted at the Clinical Trial Unit, Aarhus University [24]. Authors JDG, MK and OSS had access to the data. The Clinical Trial Unit also generated the randomization sequence using permuted blocks of 3 or 6 by computer-generated random numbers without stratification. All trial personnel were blinded to randomization.

2.3. Trial procedures

Participants were clinically assessed daily by trial personnel until day 5, and at day 14 and 30. If participants were discharged prior to day 5, the remaining study medication was given to participants for self-administration. After discharged, phone interviews were conducted up to day 30 to monitor treatment adherence and clinical status. The primary outcome was based on a 7-point ordinal scale as recommended by the WHO R&D Blueprint expert group [25]. The scale consisted of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring high-flow oxygen therapy or noninvasive ventilation; 6, hospitalized, requiring invasive mechanical ventilation; and 7, death. Oropharyngeal swabs (all participants) and blood samples (subset of participants) were obtained at baseline prior to start of study medication and on day 5 after the last dose of study medication. Swabs, serum and plasma samples were stored at −80 °C.

2.4. Outcomes

The primary endpoint was time to clinical improvement, defined as live hospital discharge or an improvement of at least 2 points from baseline on the 7-point ordinal scale, which ever came first. Secondary endpoints were: (1) safety; (2) 30-day mortality; (3) change in the National Early Warning Score 2 (NEWS2) from baseline to day 5; (4) need for supplemental oxygen and invasive mechanical ventilation during admission; (5) duration of supplemental oxygen during admission; (6) admission to the intensive care unit (ICU); (7) admission to the ICU and/or died and (8) hospital re-admission. Safety data were recorded at every trial visit and reported until day 30. The Common Terminology Criteria for Adverse Events (CTCAE) v4·03 grading scale was used to grade adverse events. A serious adverse event was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or was medically significant. The following tertiary endpoints were assessed at baseline and day 5: (1) SARS-CoV-2 viral load in oropharyngeal swabs using digital droplet PCR; (2) Plasma inflammatory biomarkers by multiplex immunoassay (VPLEX (54-plex), Meso Scale Discovery, USA). For assay details, see supplementary appendix.

2.5. Concomitant treatment

The outcomes of the ACTT-1 trial with remdesivir [12] and results of the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial investigating dexamethasone [26] were published during this trial. Therefore, some patients received remdesivir and/or dexamethasone as standard of care. All participants also received prophylactic or therapeutic anticoagulatory treatment.

2.6. Statistical analysis

The sample size calculation was based on the primary endpoint. In March 2020, when the clinical protocol written and approved, results from a trial from Wuhan indicated that the median time to reach clinical improvement in hospitalized Covid-19 patients was 16 days from admission [11]. It was anticipated that 75% of participants would reach the primary endpoint during a 30-day period [27]. Arms A (placebo) and B (camostat mesilate) were compared in a 1:2 ratio. Based on a two-sample mean comparison of A *vs* B with null-hypothesis $H0 : \delta A = \delta B$ and expected values of 16 and 12 days, respectively, and a standard deviation of 7 days, a power of 80% would be achieved with enrolment of 36 and 72 evaluable participants in arms A and B, respectively, at a 5% significance level. Considering the anticipated 25% participants that would not reach this endpoint within a 30-day period, and 20% drop-out, the aim was to enroll 60 study participants in arm *A* and 120 study participants in arm *B*, and hence 180 in total.

Kaplan-Meier survival curves were constructed for the primary outcome and compared with log-rank test. The primary analysis was conducted both as modified intention-to-treat ([*m*ITT], excluding those who never received a single dose of study medication) and per-protocol analysis excluding those who received < 80% of the planned doses of study medication. Hazard ratios with 95% confidence intervals (CI) were estimated by Cox proportional-hazards model with and without adjustment for potential confounders (oxygen supplemental at baseline, duration of symptoms prior to admission, receiving remdesivir and/or dexamethasone). Patients were censored at date of death, loss to follow-up (4 participants were lost to follow-up; Fig. 1) or end of trial, whichever came first. Stratified analyses were used to explore potential differences in effect of the intervention among subgroups (+/- oxygen supplemental at baseline, +/- remdesivir, treatment and +/- dexamethasone treatment). We considered a two-sided α value of less than 0·05 significant. Statistical analyses were performed with SAS EG software, version 8·2·1223 (SAS Institute).
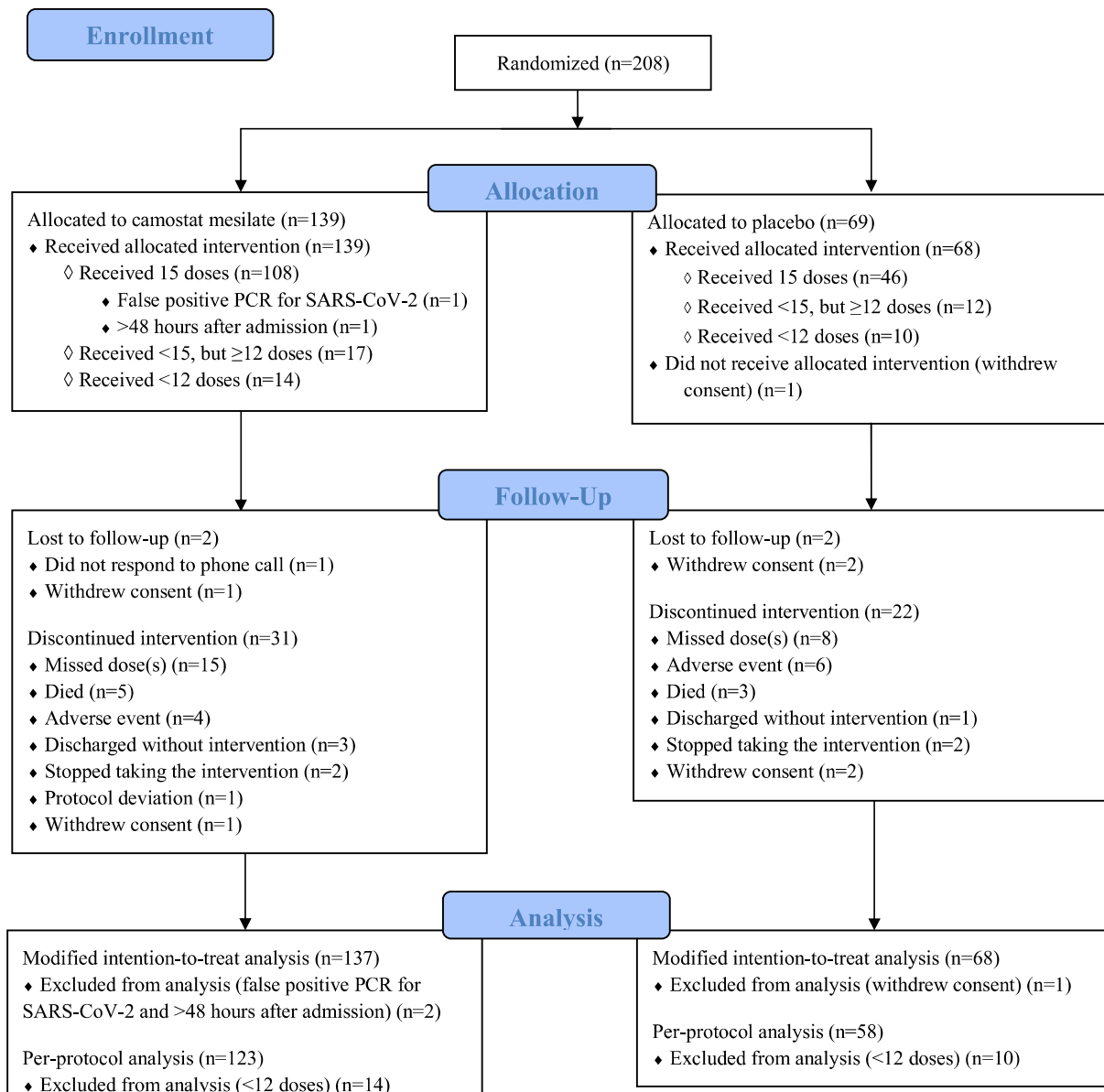
CONSORT 2010 Flow Diagram

Fig. 1. CONSORT 2010 flow diagram.

2.7. Role of funding source

3. Results

3.1. Patients

Between April 4 and December 31, 2020, a total of 208 participants were enrolled; 139 were assigned to camostat mesilate, and 69 to placebo (Fig. 1). Two participants in the camostat group, one with false positive SARS-CoV-2 PCR and one enrolled > 48 h after hospital admission, as well as one participant in the placebo group, who withdrew consent before receiving study medication, were excluded from the mITT population. Baseline characteristics

of the mITT population are shown in Table 1. In total, 123 participants (60%) were males and 82 participants (40%) were females. The median age was 61 years (interquartile range [IQR], 52 to 75). The youngest participant was 18 years of age, and the oldest was 98 years of age.

The median duration of symptoms prior to enrollment was 8 days (IQR, 6 to 11). At baseline, 136 (67%) received oxygen supplementation. Further, 33% of the participants had a body-mass index $\geq$ 30, 34% had hypertension, and 17% had diabetes mellitus. The median baseline concentration of C-reactive protein was 66·7 mg per liter (range, 0·1 to 310·0); and ferritin was 478 μg per liter (range, 4 to 11,350).

During the trial, similar proportions of participants in the two groups received remdesivir and/or dexamethasone. Remdesivir was administered to 96 participants; 64 (47%) in the camostat group and 32 (47%) in the placebo group. Dexamethasone was administered to 124 participants; 82 (60%) in the camostat group and 42 (62%) in the placebo group.

Table 1
Baseline characteristics at study entry

Characteristics	Camostat mesilate (n=137)	Placebo (n=68)	Total (n=205)
Median age (IQR) – yr	62 (51–75)	61 (55–74)	61 (52–75)
Male sex – no. (%)	82 (60)	41 (60)	123 (60)
Median time (IQR) from symptom onset to baseline – days	8·0 (6·0–11·0)	8·0 (5·0–11·5)	8·0 (6·0–11·0)
Median weight (IQR) – kg[¥]	85 (73–95)	90 (79–101)	87 (75–100)
Median body–mass index(IQR) – kg/m2[¥]	27·4 (24·4–31·6)	28·8 (26·0–32·9)	27·7 (25·0–32·2)
Obesity – no. (%)[§]	37 (27)	30 (44)	67 (33)
Symptoms – no. (%)			
Cough	116 (85)	58 (85)	174 (85)
Dyspnea	95 (70)	42 (62)	137 (67)
Fatigue	119 (87)	62 (91)	181 (88)
Headache	71 (52)	36 (53)	107 (52)
Coexisting conditions – no. (%)			
Asthma	18 (13)	9 (13)	27 (13)
COPD	14 (10)	7 (10)	21 (10)
Coronary heart disease	29 (21)	10 (15)	39 (19)
Hypertension	50 (36)	21 (31)	71 (34)
Malignancy	20 (15)	9 (13)	29 (14)
Type 2 diabetes	21 (15)	14 (21)	35 (17)
Score on 7–point ordinal scale – no. (%)			
3. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	47 (34)	22 (32)	69 (33)
4. Hospitalized, requiring supplemental oxygen	81 (59)	39 (57)	120 (59)
5. Hospitalized, requiring high–flow oxygen therapy or noninvasive ventilation	9 (07)	7 (10)	16 (08)
Candidate for intubation – no. (%)	119 (87)	61 (90)	180 (88)
Resuscitation candidate – no. (%)	117 (85)	60 (88)	177 (86)
National Early Warning Score 2 – median (IQR)	4 (3–6)	4 (2–5)	4 (2–6)
Viral load in nasopharyngeal swab (baseline)			
Log10 scale			
Patients – no. (%)	122 (88)	60 (88)	182 (88)
Mean±sd viral load – copies/ml	4·6 ±1·8	4·9 ±1·7	4·5 ±1·7
Median viral load (range) – copies/ml	4·4 (2·3–8·7)	4·8 (2·3–8·2)	4·4 (3–5·8)
Serum C–reactive protein level			
Mean±sd leve l– mg/liter[*]	88·2 ±71·1	73·0 ±68·7	83·2 ±70·5
Median level (range) – mg/liter	68·8 (0·7–310·0)	56·0 (0·1–288·8)	66·7 (0·1–310·0)
Serum ferritin			
Mean±sd level – μg/liter[*]	714·8 ±604·0	791·6 ±1,482·0	740·1 ±980·7
Median level (range) – μg/liter	485 (4–2689)	404 (15–11,350)	478 (4–11,350)

IQR denotes interquartile range, COPD chronic obstructive pulmonary disease, and sd standard deviation.
  [¥] Data on weight and body–mass index were missing for 5 and 6 patients in the camostat group.
  [§] Obesity is defined as a body–mass index of greater than 30.
  [*] Data on serum C–reactive protein/ferritin levels were missing for 2/9 and 1/5 patients in the camostat and placebo group.

3.2. Primary outcome

A total of 191 participants (93%) experienced a clinical improvement of ≥ 2 points on the 7-point ordinal scale within 30 days of enrollment (Fig. 2, Table S1). The Kaplan−Meier curves for time to clinical improvement are shown in Fig. 3. In the mITT population, median time to clinical improvement was 5 days (IQR, 3 to 7) in the camostat group and 5 days (IQR, 2 to 10) in the placebo group (log-rank test, $P = 0.37$). A total of 10% of participants in the camostat group and 14% in the placebo group received $< 80\%$ of the planned doses of study medication. Discontinuation of study treatment was primarily due to adverse events (38%), discharge without study medication (17%) and withdrawal of consent (17%). In the per-protocol population, median time to clinical improvement was 5 days (IQR, 3 to 8) in the camostat group and 5 days (IQR, 2 to 10) in the placebo group ($P = 0.92$). The unadjusted hazard ratio for clinical improvement in the camostat group was 1·14 (95% CI, 0·84 to 1·55; $P = 0.40$ by Cox regression). The hazard ratio adjusted for duration of symptoms, oxygen supplementation at baseline, remdesivir and dexamethasone treatment was 1·14 (95% CI, 0·84 to 1·59). Stratifying study participants according to remdesivir and/or dexamethasone treatment did not impact the effect of camostat on time to clinical improvement (Fig. 3E,F and Fig. S1).

3.3. Secondary outcomes

A total of 26 participants (13·1%) were intubated or died within 30 days (Table S2), 14 participants (10%) in the camostat group and

12 (18%) in the placebo group. The Kaplan−Meier curve for time to ICU admission or death is shown in Fig. S1. The combined hazard ratio for intubation or death in the camostat group as compared with the placebo group was 0·54 (95% CI, 0·25 to 1·18; $P = 0.12$) and the hazard ratio for death alone was 0·70 (95% CI, 0·17 to 2·15; $P = 0.58$). The median duration of oxygen supplementation from baseline was 4 days (IQR, 2 to 7) in the camostat group and 4 days (IQR, 2 to 8) in the placebo group. Median time from enrollment to hospital discharge was 5 days (IQR, 3 to 8) in the camostat group and 6 days (IQR, 3 to 11) in the placebo group. No significant change in the National Early Warning Score (NEWS) 2 was observed from baseline to day 5 ($P = 0.93$).

3.4. Tertiary outcomes

Overall, baseline viral loads were higher among participants with short symptom duration compared to those with a longer symptom duration (Fig. 4A). Among participants with paired samples available (Fig. 4B), the median change in viral load from baseline to day 5 in the camostat group was -0.22 $\log_{10}$ copies per mL ($p < 0.05$) and -0.76 $\log_{10}$ copies per mL in the placebo group ($P < 0.05$). In the camostat group (Fig. 4C), the median change in viral load from baseline to day 5 among those also receiving remdesivir was -0.10 $\log_{10}$ copies per mL ($p = 0.98$) and -0.75 $\log_{10}$ among those only receiving camostat ($P < 0.001$). Within the placebo group, the magnitude of change in viral load among those receiving remdesivir or no remdesivir was comparable (Fig. 4D).
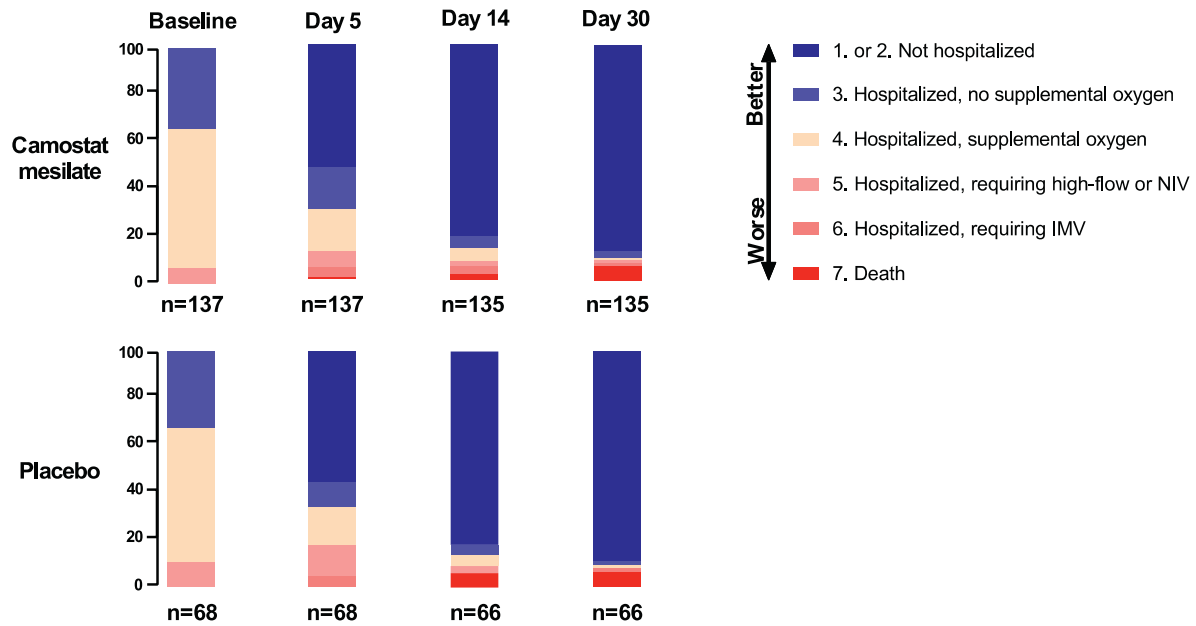
Fig. 2. Score on 7-point ordinal scale over time. Cumulative percentage of 7-point ordinal scale at baseline, day 5, 14 and 30 in the camostat mesilate and placebo group (Table S1 for absolute numbers). IMV denotes invasive mechanical ventilation, and NIV noninvasive ventilation.

Changes in inflammatory levels were evaluated by profiling of 54 inflammatory biomarkers in paired samples from 65 randomly selected participants; 41 in camostat group, 24 in placebo group (Fig. 4E). The inflammatory markers were not different between treatment groups at baseline, at day 5, nor as log2 ratio between baseline and day 5 (Fig. 4F).

3.5. Safety

A total of 60 patients experienced adverse events during the trial, 38 (28%) in the camostat group and 22 (32%) in the placebo group (Table S3). There were 27 (20%) serious adverse events in the camostat group and 8 (12%) in the placebo group. No serious adverse events were considered related to study medication (Table S4).

4. Discussion

The hypothesis underlying our trial was that TMPRSS2 inhibition would block SARS-CoV-2 replication in infected patients leading to reduced viral loads, and that this in turn would lower the risk of hyper-inflammation and prevent disease progression. However, our results show that among patients hospitalized with Covid-19 camostat mesilate treatment did not significantly improve time to clinical improvement, the risk of intubation or death, time to discontinuation of supplemental oxygen, or any other efficacy outcomes.

The findings from our randomized trial contrast those of non-randomized case series, some of which have suggested that TMPRSS2 inhibition had remarkably beneficial effects on the outcome of Covid-19 [23,28,29]. The reasons for the failure of camostat mesilate to improve clinical outcomes substantially in our trial are not clear. One possibility is that most of the participants had passed the most active stage of viral replication on admission and were at the hyper-inflammatory stage of the disease. [8,16] The median duration of symptoms prior to enrollment in our study was 8.5 days. The current consensus on the treatment of Covid-19 is that antiviral drugs need to be administered early during the viral replication phase to impact the clinical outcome. [13,16,30] Thus, among those with longer symptom duration, the potential antiviral effect of camostat mesilate may have little impact on already elevated plasma levels of interleukin-6 and other pro-inflammatory proteins that drive disease progression at the

hyper-inflammatory stage. Another possibility is that the plasma concentration of camostat mesilate and its metabolites were too low to substantially inhibit TMPRSS2. If so, the spike protein would still be able to be cleaved by TMPRSS2 allowing for virus cell entry and replication [20]. Regardless of the explanation, our findings largely undermine the concept that camostat mesilate is a useful treatment strategy for reducing the severity and duration of moderate to severe Covid-19. Our findings also emphasize that any repurposing of approved drugs for treatment Covid-19 must be investigated in randomized, blinded trials before being taken into widespread off-label use as a new treatment strategy.

It remains possible, however, that patient populations that differ from the one targeted by our trial might benefit from camostat mesilate. It is also possible that other TMPRSS2 inhibitors such as nafamostat or gabexate will show efficacy. Our results confirmed the excellent safety profile of camostat mesilate. The proportion of adverse events and serious adverse events was low in the camostat group and at the same level as in the placebo group. The safety data further support that the intervention was safe and well tolerated. In addition, our data confirmed that patients with short duration of symptoms generally had much higher viral load than patients with longer duration of symptoms.

Our trial has a number of strengths. It was an investigator-initiated, double-blind, randomized, placebo-controlled trial with successful randomization as supported by the ratio of included patients in the two trial arms, and the similarity of the unadjusted and adjusted hazard ratios. The trial also had limitations. The observed time to clinical improvement was shorter than anticipated, perhaps because of evolving standards of care since the early days of the pandemic: these included the availability of the drugs remdesivir and dexamethasone as well as improved management strategies such as delayed intubation instead of the early intubating strategy generally applied in the early epidemic. There is a risk of type II error with the shorter observed time to clinical improvement. Nevertheless, 11% of the patients in our trial were admitted to an ICU or died high-lighting the severity of Covid-19 in our study population. Although there was a trend towards lower risk of ICU admission/death in the camostat group, the trial was not powered to address this endpoint and the result should be interpreted with caution.
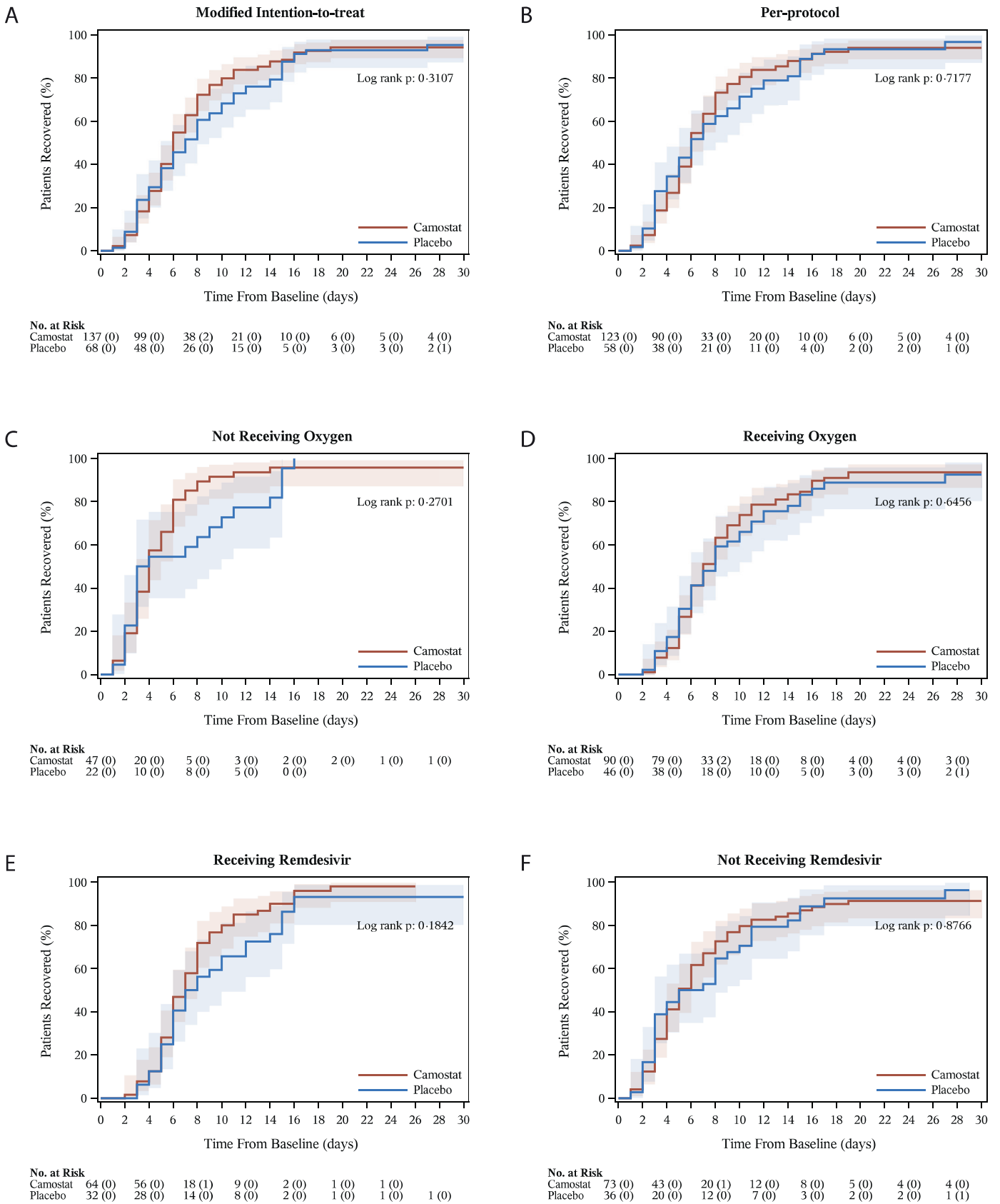
Fig. 3. Kaplan-meier estimates of cumulative recoveries. Cumulative recovery estimates are shown in the modified intention-to-treat population (Panel *A*), in the per-protocol population (Panel *B*), in patients with a baseline 7-point ordinal scale of 3 (hospitalized, not requiring supplemental oxygen; Panel *C*), in those with a baseline 7-point ordinal scale of 4 (requiring supplemental oxygen; Panel *D*), in those receiving remdesivir during admission (Panel *E*), and in those not receiving remdesivir during admission (Panel *F*).
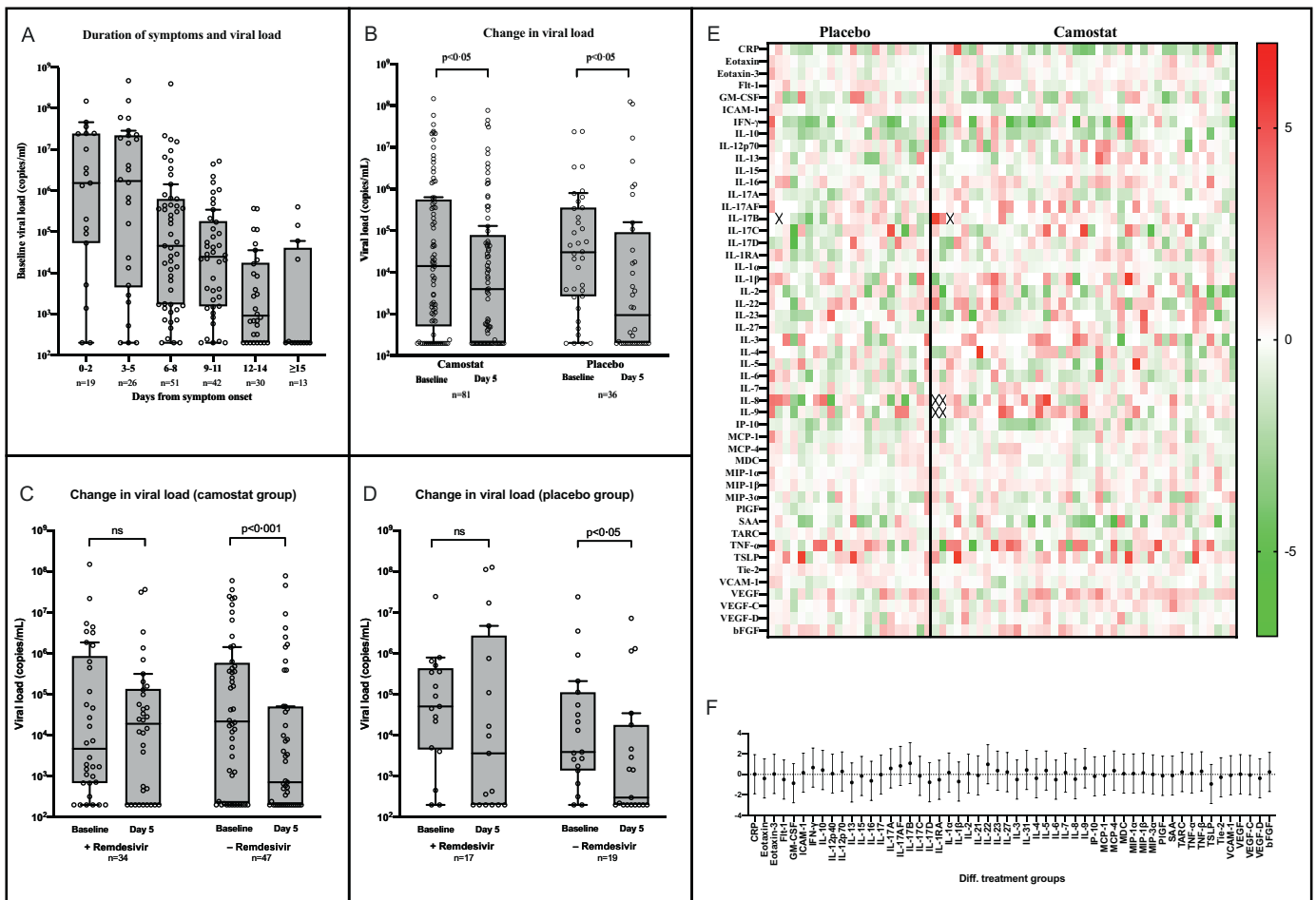
Fig. 4. SARS-CoV-2 viral load and cytokine profiling at baseline and day 5. The baseline viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in oropharyngeal swab decreases (in log10 copies per milliliter) in overall population according to longer time since onset of symptoms (Panel *A*). SARS-CoV-2 viral load for each patient per group and group median (interquartile ranges and 1.5 times IQR whiskers) are shown in Panel *B* for camostat mesilate and placebo groups, and in camostat mesilate (Panel *C*) or placebo (Panel *D*) group receiving either remdesivir or not. The lower limit of quantification was set to 200 copies/ml. Plots show median values (line) and 25th to 75th percentiles (box). Wilcoxon signed-rank test was used to compare median between groups. Cytokine profiling of 65 patients, 24 receiving placebo and 41 receiving camostat mesilate. Values are log2 transformed ratio between day 5 and 1 for individual patients. Heatmap of log2 transformed day 5-to-1 ratio of individual patients in the two treatment groups (Panel *E*). 'X' indicates missing value. Comparison between cytokine mean change between treatment groups (camostat mesilate-placebo) were analyzed using 2-way ANOVA, and Šidák's multiple comparison test (Panel *F*). IL3, IL17, IL21, and IL31 did not meet quality criteria and were omitted.

Our findings show that 200 mg t.i.d. camostat mesilate is not an effective treatment for hospitalized patients with Covid-19. However, we cannot exclude the possibility that camostat mesilate treatment in a higher dose or during the very early phase of Covid-19 might be effective in lowering the risk of disease progression.

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Declaration of Competing Interest

Dr. Mortensen reports a Gilead Travel Grant, outside the submitted work. Dr Østergaard reports personal fees from GlaxoSmithKline-Pharma A/S, Gilead Science Denmark A/S, Pfizer A/S, MSD Denmark A/S, and Sanofi Pasteur Europe, outside the submitted work. Dr. Kjolby reports grants from The Lundbeck Foundation, during the conduct of the study; and has or has had stocks in Genmab, Novo Nordisk, Novartis, Amgen, and Regeneron. All other authors have nothing to disclose.

Data sharing statement

Data are not available for download due to privacy/ethical restrictions under the EU GDPR. Specific requests for access to the trial data may be sent to olesoega@rm.dk and access may be provided to a named individual in agreement with the rules and regulations of the Danish Data Protection agency and the National Committee on Health Research Ethics.

Author contributions

JDG, MK and OSS developed the design. JDG, NBS, LHK, JB, NL, LSD, DB, OF, BH, ISJ, EM, TM, DGB, RO, SS, SC, NPJ, SSS, SJ, KLM, MLJ, LK, GSF, CSL, MS, LØ, JFH and OSS did the clinical visits. MHP, CE, RR, PB, LPN, MT, EAS and HTTN did the laboratory assays. JDG, MHJ, MK and OSS analyzed data. JDG, MK and OSS drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100849.

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