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Camostat mesylate against SARS-CoV-2 and COVID-19—Rationale, dosing and safety

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Abstract

The coronavirus responsible for COVID-19, SARS-CoV-2, utilizes a viral membrane spike protein for host cell entry. For the virus to engage in host membrane fusion, SARS-CoV-2 utilizes the human transmembrane surface protease, TMPRSS2, to cleave and activate the spike protein. Camostat mesylate, an orally available well-known serine protease inhibitor, is a potent inhibitor of TMPRSS2 and has been hypothesized as a potential antiviral drug against COVID-19. In vitro human cell and animal studies have shown that camostat mesylate inhibits virus-cell membrane fusion and hence viral replication. In mice, camostat mesylate treatment during acute infection with influenza, also dependent on TMPRSS2, leads to a reduced viral load. The decreased viral load may be associated with an improved patient outcome. Because camostat mesylate is administered as an oral drug, it may be used in outpatients as well as inpatients at all disease stages of SARS-CoV-2 infection if it is shown to be an effective antiviral agent. Clinical trials are currently ongoing to test whether this well-known drug could be repurposed and utilized to combat the current pandemic. In the following, we will review current knowledge on camostat mesylate mode of action, potential benefits as an antiviral agent and ongoing clinical trials.

KEYWORDS

Antiviral drugs < Viral infections, Camostat mesylate, drug repurposing, Infection < Immunotoxicology, Lung, pulmonary or respiratory system < Respiratory toxicology, tmprss2

1 | INTRODUCTION

SARS-CoV-2 is a new coronavirus with epicentre in the Hubei-region in China from where it spread globally in late 2019.[1-3] As of 11 March 2020, WHO declared the situation a pandemic.[4] Infection with SARS-CoV-2 leads to COVID-19, a disease ranging from mild respiratory illness to fatal pneumonia with acute respiratory distress syndrome (ARDS).[2,5] SARS-CoV-2 has proven highly contagious and has put an immense strain on healthcare systems worldwide.

To avoid national health systems succumbing to the large patient load with the inevitable increments in patient mortality, WHO recommended a rapid case identification, testing and isolation strategy on 14 April 2020. This is to be followed by comprehensive contact tracing and quarantine of contacts. So far, this approach has been associated with lower hospitalization rates and fatality in countries enforcing this strategy. Government responses have ranged from travel restrictions to essentially complete shutdown of numerous countries around the globe.

As social distancing is not a viable long-term stand-alone strategy, pharmacological treatment of infected patients is necessary until herd immunity is reached by widespread viral outbreaks or an effective prophylactic vaccine. As of November 2020, only corticosteroids have proven conclusively successful in the treatment of COVID-19 with dexamethasone reducing overall 28-day mortality in hospitalized patients with severe COVID-19. In patients with invasive mechanical ventilation, dexamethasone treatment reduced lethality from 41.1% in placebo group to 28.3% in the treatment group, whereas no effect was found when patients did not receive respiratory support at randomization.[6] Initially, Remdesivir was found to shorten the duration of hospitalization[7] but in a yet to be peer-reviewed study, the intravenous drug was found to be ineffective (n = 2750) alongside hydroxychloroquine (n = 954), Lopinavir (n = 1411) and interferon (n = 1412 and in combination with Lopinavir: n = 651) in a large international randomized study on more than 11 000 inpatients in 30 countries.[8] On 22 October 2020, Remdesivir received full FDA approval as treatment of COVID-19 in hospitalized adults and paediatric patients (older than 12 years and weighing at least 40 kg) but with the inconsistent findings and intravenous delivery method, out-patient use of the drug is complicated and questionable. Moreover, a global backorder and high cost adds to the complexity of broad treatment with Remdesivir.

The viral replication cycle has been thoroughly studied for the closely related coronavirus SARS-CoV, the cause of the 2002-2003 severe acute respiratory syndrome (SARS) outbreak, and to a lesser degree for SARS-CoV-2.[9-12] Here, new pharmacological targets have emerged. Of particular interest is the viral host cell entry mechanism. Blocking viral host cell entry will efficiently stop viral replication and disease progression. Camostat mesylate is a serine protease inhibitor that shows promise in cell cultures in combating SARS-CoV-2 through limiting viral entry. Camostat mesylate has been clinically used for treatment of pancreatitis and reflux oesophagitis for over two decades.[13] The drug has few and mild side effects even at high dosages[14,15] and is readily produced at low costs. Our goal is to review current knowledge on camostat mesylate and the pharmacological actions that may prove fruitful in combating SARS-CoV-2 and the COVID-19 pandemic.

2 | SARS-COV-2 AND COVID-19

SARS-CoV-2 is an enveloped positive-strand RNA virus (+ssRNA virus) that transmits from person-to-person through respiratory droplets and by direct contact.[16,17] The initial infection is presumed to occur in the mucosal epithelium in the upper respiratory tract. In milder cases, the infection is controlled by the immune system at this point, but a further involvement of the lung is often observed.[18] The helical nucleocapsid is surrounded by a viral envelope that holds a two-subunit spike protein.[19] The outer S1-subunit of the spike enables receptor binding whereas the S2 subunit enables membrane fusion (Figure 1). Upon interaction between the mucosal epithelial cell and virus, the S1 subunit binds to the host cell angiotensin-converting enzyme 2 (ACE2) receptor.[10,12,20] The specificity to the ACE2-receptor and the host proteases leads the virus to primarily replicate in the epithelium of the lung and respiratory tract[21] where ACE2 protein expression is high[22] especially in the lower respiratory tract.[18] As SARS-CoV-2 closely resembles SARS-CoV, it has been hypothesized that many of the SARS-CoV viral cell entry mechanisms also apply to SARS-CoV-2.[11,23,24]

Upon ACE2 binding, the SARS-CoV-2 spike proteins are proteolytically processed at the S1/S2- and S2 sites by host proteases.[11,12] The proteases at the cell surface include furin,[25] the cell surface proteases TMPRSS2 and to a minor degree TMPRSS13, TMPRSS11D, −11E and 11F.[26] The lysosomal proteases include cathepsin L/B (Figure 1).[12,19,26-28] However, this pathway is only active to a minor extent.[12,26] Consequently, the internal fusion machinery in the spike protein is activated and mediates fusion of cell/vesicle membrane and virus envelope, thus the nucleocapsid is released to the host cell cytoplasm where the virus starts replicating.[27] During infection, the virus may trigger release of pro-inflammatory cytokines including IL-8, IL-6 and TNF-α leading to tissue damage with subsequent vascular leakage.[24] If left uncontrolled, this disease process can give rise to a cytokine release storm with lymphocyte infiltration.[24,29] This picture, similar to macrophage activation syndrome (MAS), can thus lead to lung tissue damage and oedema eventually resulting in life-threatening respiratory failure.[24] Furthermore, the virus may be able to downregulate and shed ACE2.[18,24] This can result in dysfunction of the pulmonary renin-angiotensin-system, causing vascular permeability and further complicating the inflammatory state.[18,23]

3 | CAMOSTAT MESYLATE INHIBITS SARS-COV-2 HOST CELL ENTRY

As viral load may be associated with negative outcome, restricting viral cell entry and thereby reducing of overall viral

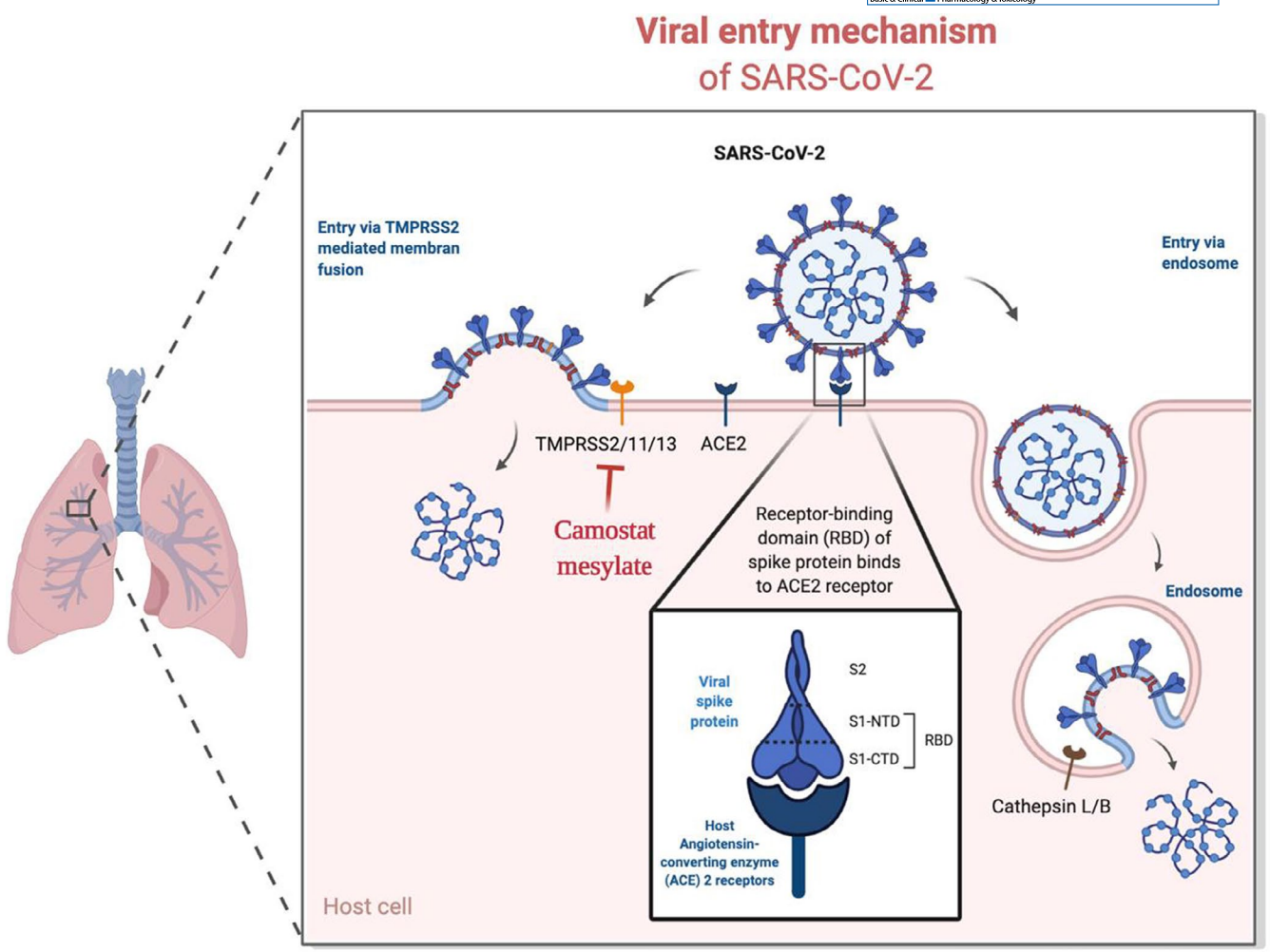

FIGURE 1 Illustration of SARS-CoV-2 entry mechanisms. Viral host cell entry through airway epithelium is initiated by the receptor-binding domain (RBD) of the viral spike protein binding to host cell angiotensin-converting enzyme 2 (ACE2). Upon ACE2 binding, the spike proteins are proteolytically processed by host proteases in either lysosomal vesicles after endocytosis or at the cell surface. The cell surface entry mechanism has proven the most efficient and is mediated by Transmembrane Serine Proteases (TMPRSS). These can be blocked by serine protease inhibitors like camostat mesylate efficiently reducing host cell viral uptake

load could slow disease progression. This, in turn, increases the timespan in which the innate and adaptive immune system can combat the virus resulting in reduced cytokine-mediated tissue damage. Reducing viral and host cell membrane fusion is more efficient for viral entry reduction than endosomal pathway inhibition.[12,26,30]

A candidate drug to reduce viral host cell entry is camostat mesylate. Camostat mesylate is attractive as an antiviral agent, as it inhibits many of the serine proteases that SARS-CoV and SARS-CoV-2 use for virus-to-host cell membrane fusion, like TMPRSS2, −13, and −11D/E/F (Figure 1).[26,31,32] The lack of extracellular proteases like TMPRSS2 reduces cellular infection rate of SARS-CoV more than 100-fold[33] making these proteases a convincing target when combating SARS-CoV-2 infection. Using camostat mesylate to block virus-membrane fusion may diminish viral infection by two thirds[32] and hence reduce the likelihood of severe infection and the accompanying morbidity and mortality. The knock-on effect of reducing patient days of hospitalization could ease the burden on healthcare systems and enable reduction in stringency of government restrictions.

A preclinical animal study showed that when mice are given a fatal dose of SARS-CoV, lethality can be reduced by 60% with twice daily administration of 30 mg/kg camostat mesylate.[30] In vitro studies of SARS-CoV-2 in a human lung cell line and primary human lung epithelial cells have revealed significant reduction in SARS-CoV-2 spike protein driven cellular entry.[12] Cell entry in a human colon epithelium cell line by SARS-CoV-2 spike protein expressed pseudotyped-virus is partially blocked by camostat mesylate. In a primate kidney epithelium cell line, camostat mesylate is efficient in blocking spike protein-induced fusion only when TMPRSS2 is present,[12] emphasizing the importance of this specific protease for the action of camostat mesylate.

4 | CAMOSTAT MESYLATE MODE OF ACTION

Camostat mesylate is a potent inhibitor of TMPRSS2, −13, and 11D/E/F.[26] TMPRSS2 is a type II transmembrane serine protease that is widely expressed in epithelial cells but with a yet unknown physiological function. The protease has been shown to facilitate cell entry of numerous viruses including influenza, SARS and MERS.[12,30,31,34,35] Whereas furin cleaves the spike protein at the S1/S2 site, TMPRSS2 cleaves it at the 2′ site, which has been proposed to activate the membrane fusion activity of the spike protein.[25,36] Multiple TMPRSS2 inhibitors have been proven efficient in combating SARS-CoV-2 infection in vitro confirming TMPRSS2 as being a key mediator of viral entry.[25]

Upon human oral dosing, camostat mesylate is a prodrug which has a short plasma half-life of <1 minute.[13,37] Hydrolysis of the dimethyl acetamide side-chain ester group in ex vivo plasma preparations and in vivo, in the gut or readily after systemic uptake, produces GBPA (4-(4-guanidinobenzoyl-oxy)phenylacetic acid)[37] also known as FOY-251. GBPA is equally potent inhibitor of TMPRSS2 and distributes to well-perfused organs including the lungs.[26,37] The half-life of GBPA after intravenous infusion of the parent drug is roughly an hour before being metabolized to GBA which is not a TMPRSS2 inhibitor.[37]

Based on the accepted inhibition of the enzymatic catalytic mechanism and the available X-ray crystal structure derived picture of camostat mesylate soaked in Prostasin (PDB 3FVF) (Figure 2), also a serine protease, it is known that camostat mesylate or GBPA bind in the protease active site.[38] Here, camostat mesylate or GBPA is cleaved by the triad His85-Asp134-Ser238 (corresponding to His296-Asp345-Ser441 in human TMPRSS2), forming a covalent bond between the carboxy warhead of GBA and serine 238.[38] It is not known whether the observed covalent bond (in 3FVF) results similarly in an irreversible inhibition of TMPRSS2, which then should be taken into account when determining dosing and timing in relation to TMPRSS2 turnover. In silico, modelling of the TMPRSS2-targeting camostat mesylate and bromhexine in the TMPRSS2 model structure predicts that the complete or "intact" camostat mesylate structure fits across the three, proposed, sub-pockets, namely the S1 (oxyanion hole), the catalytic triad domain and the hydrophobic patch.[39] Furthermore, the models predict efficient hydrogen bonding and Van-der-Walls interactions of camostat mesylate across the three domains (eg Asp435 at S1, catalytic Ser441 and His296 at the distal hydrophobic patch). By comparison, bromhexine is predicted to bind at the hydrophobic patch domain only.[40,41] Thus, rationalizing the in vitro inhibition constant (Ki) of 1.51 μM compared with 43.00 μM (camostat mesylate vs bromhexine). Camostat mesylate is therefore the theoretically more potent binder of the two drugs in terms of SARS-CoV-2 host virus-membrane fusion inhibition. However, by analogy to recently[42] and previously reported studies, camostat mesylate and its active metabolite GBPA are expected to be, not only competitive inhibitors of TMPRSS2, but also substrates leading to covalent inhibition.[38,42] Further experimental work is necessary to establish the exact nature and molecular mechanism of inhibition of TMPRSS2 by camostat mesylate and GBPA, establishing the relevance of its pseudo irreversible inhibition[38] for human PK-PD modelling. In vivo plasma profile of GBPA, the metabolic substrate of camostat mesylate, may be the more relevant species binding to the enzyme. Studies are, equally, needed to understand, in silico, the GBPA binding mode, as a critical step to design superior in vivo analogues of GBPA. The understanding of the human whole-body pharmacokinetics and—dynamics may prove more important than binding affinity and—strength in the target organ.

5 | CAMOSTAT MESYLATE AS A TREATMENT OPTION DURING INFECTION

Based on the current knowledge of SARS-CoV-2 spike protein-mediated host membrane fusion, the use of camostat mesylate as a prophylactic or early phase COVID-19 treatment option is compelling. However, as influenza virus also use serine proteases such as TMPRSS2 for host cell entry, some additional knowledge can be gained from studies on camostat mesylate in influenza virus infection in human epithelial cell cultures. These indicate a reduction in viral replication even if treatment is initiated after host cell infection.[35] Furthermore, camostat mesylate reduced the inflammatory markers IL-6 (7-fold) and TNF-α (3-fold) in the cell supernatants compared with non-treated controls five days post-infection. As COVID-19 disease progresses, the viral titre may not correlate with the severity of disease.[43,44] This indicates that immunopathological processes may worsen the condition and, in some cases, cause a potentially fatal cytokine storm. For SARS-CoV infection, and possibly also for SARS-CoV-2,[44] further lung damage and worsening of the disease can be seen even at low viral loads. Indeed, antiviral treatment should preferably be started as soon as possible before the inflammatory cytokine storm is accompanied by immunopathogenic changes and the damage becomes too extensive.[29] However, there may still be a reason for camostat mesylate treatment initiation after onset of severe COVID-19. SARS-CoV spikes are potent stimulators of the pro-inflammatory cytokine transforming growth factor-beta (TGF-β).[45,46] As seen during other uncontrolled cytokine storms, TGF-β has been shown to play an important part in progressive fibrosis in COVID-19-mediated ARDS.[47] TGF-β has therefore been proposed as a relevant pharmacological

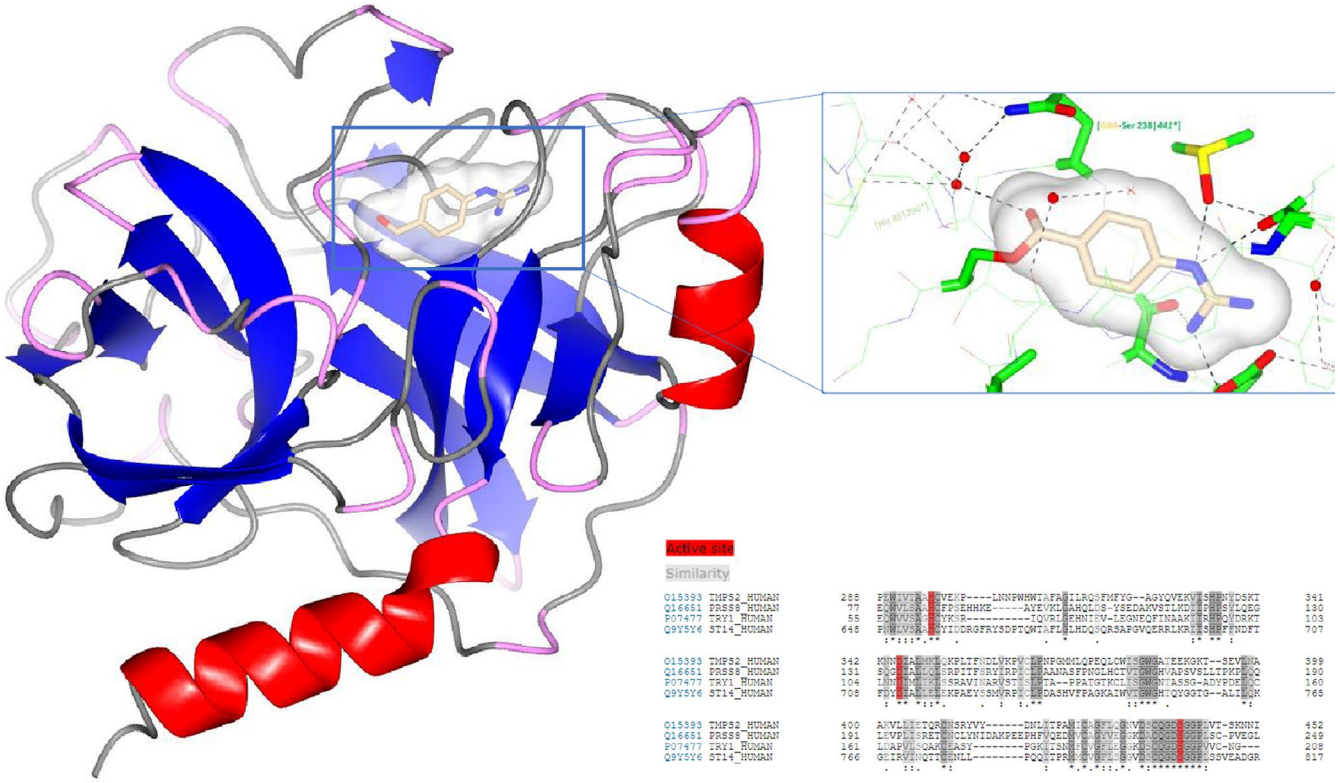

FIGURE 2 Camostat metabolite GBA binding to serine protease. Crystal structure of prostasin (3FVF) with camostat metabolite GBA covalently bound in the active site. Camostat mesylate and GBPA can be cleaved to form GBA. This cleavage process forms a covalently bound GBA to Serine in the active site. There is high similarity of the active site between the serine proteases, TMPRSS2 (TMPS2), Prostasin (PRSS8), Trypsin (TRY1) and Matriptase (ST14) that are all targets of camostat mesylate

target in the pandemic.[48] Studies in laboratory animals have revealed that camostat mesylate reduces TGF-β and accompanied fibrosis[49] increasing the likelihood of camostat mesylate to alleviate COVID-19-induced ARDS.

6 | CAMOSTAT MESYLATE SAFETY

Camostat mesylate has been thoroughly tested and used as a human therapeutic for more than two decades[14] (Table 1). It is primarily used for symptomatic relief for conditions in the upper gastrointestinal tract. When used in the treatment of acute worsening of chronic pancreatitis or postoperative reflux oesophagitis, the recommended dosage is 300-600 mg/day in three dosages of 100-200 mg.[13] The side effects are usually mild and include rash and pruritus (<0.5%), nausea or abdominal discomfort (<0.5%) and liver enzyme elevation (<0.5%). Common for the side effects is that they cease when drug administration is discontinued.[13,15] This may be true even for much higher dosages, as no significant side effects were seen in 9 patients treated with 7.2 g/day for up to 8 months.[14] With adverse effects generally being mild even at very high dosages for prolonged periods of time, the most important aspect, if camostat mesylate is to be used in combating COVID-19, is to reach the plasma concentration sufficient to inhibit viral replication.

7 | CAMOSTAT MESYLATE DOSING IN COVID-19

Camostat mesylate reduces SARS-CoV-2 cell entry in cell cultures by 50% (EC_{50}) at a concentration of 1 μM and 90% at 5 μM (EC_{90}).[12] If in vitro data are translatable, the concentration in the lungs needs to surpass 1 μM to achieve 50% effective concentration. However, in vitro studies in Influenza A/H1N1 (responsible for the 2009 pandemic) and A/H3N2 infection models revealed a concentration-dependent decrease in viral supernatant titres at concentrations even lower than this. A significant reduction was found at concentrations as low as 0.01 μg/mL[35] equivalent to 0.02 μM (Table 1). Pharmacokinetic studies revealed substantial distribution of camostat mesylate/GBPA to the lungs in both rats and dogs 10 minutes after a single intravenous bolus of camostat mesylate. There was a tendency for the drug to concentrate in tissue and to eliminate at a slower rate than in plasma indicating tissue binding or uptake.[37] When reducing mortality by 60% after viral challenge with SARS-CoV in mice, camostat mesylate was dosed at 30 mg/kg twice daily.[30] Unfortunately,

TABLE 1 Camostat mesylate doses and concentrations used in *ex* and in vivo studies

Species	Study group	Dosage	Study
Human	Healthy Caucasian males	40 mg in 120 mL saline infused iv over 12 hours	Midgley, I et al[37]
Human	Case Report: A 69-year-old woman with Evans syndrome	500 mg/day	Nakao, A et al[59]
Human	Case Report: Two patients with ulcerative colitis	600 mg/day	Senda, S et al[60]
Human	Suspected pancreatic disease	200 mg × 3/day for 2 weeks	Sai, JK et al[61]
Human	Three patients with diabetic nephropathy with the nephrotic syndrome	600 mg/day	Ikeda, Y *er al*[62]
Human	Diabetic nephropathy	600 mg/day for 4 weeks (Camostat mesylate)	Onbe, T et al[63] Matsubara, M et al[64,65]
Human	Fourteen patients, age 4-16 years, with an abnormal urinalysis	100 mg × 2/day	Asami, T et al[66]
Human	Fifteen patients with a mild grade of chronic pancreatitis	200 mg × 3/day	Sugiyama, M et al[67]
Human	Patients Gastro-oesophageal reflux disease	300 mg × 3/day for 4 weeks	Kono, K et al[68]
Human	Nine patients, age 41-63 years, with squamous cell carcinoma	Up to 7.2 g/day	Ohkoshi, M et al[14]
Human	12 healthy volunteers	500 mg × 4/day for 4 weeks	Friess, H et al[15]
Human	24 patients, age (mean ± SD) 59 ± 14 years, with unexplained dyspepsia	200 mg × 3/day for 4 weeks	Ashizawa, N et al[69]
Human (cells)	Calu-3-cells and H3255 cells infected with 293FT cells expressing SARS-2-S proteins	10-100 nM	Yamamoto, M et al[70]
Human (cells)	Calu-3-cells infected with pseudotype particles bearing SARS-2-S proteins	0.01-100 μM	Hoffmann, M et al[26]
Human (cells)	Calu-3-cells infected with SARS-CoV-2. Primary human airway epithelial cells infected with pseudotype particles bearing SARS-2-S proteins	Calu-3 cells: 1-500 μM Primary cells: 10 μM and 50 μM	Hoffmann, M; Kleine-Weber, H et al[12]
Human (cells)	Calu-3-cells infected with SARS-CoV-2 or SARS-2-S bearing VSV particles	SARS-CoV-2 entry: 100 nM or 100 μM. SARS-2-S bearing entry: 1-100 μM.	Hoffmann, M; Schroeder, S et al[57]
Human (cells)	Calu-3-cells infected with SARS-CoV	10 μM	Kawase, M et al[32]
Human (cells)	Calu-3-cells infected with 293FT cells expressing MERS-S proteins	0.01, 0.1, 1 or 10 μM	Yamomoto, M; Matsuyama, S et al[71]
Human (cells)	Calu-3-cells (and other lung-derived cell lines) infected with MERS-CoV	1, 10 and 100 μM	Shirato, K et al[31]
Human (cells)	human tracheal epithelial cells infected with A/H1N1 or A/H3N2	10 μg/mL	Yamaya, M et al[35]
Mice	Mice infected with SARS-CoV	30 mg/kg × 2/day for 9 days	Zhou, Y et al[30]
Mice	Mice infected with A/H1N1	1.95 mg/mL/100 g BW, IP × 2/day for 7 days	Lee, M. G. et al[34]

plasma concentrations of camostat mesylate and metabolites were not determined in the mice. This dose (30 mg/kg) is equivalent to 2100 mg × 2 in a 70 kg human when translating dose per weight. If dose is translated on the basis of body surface area, which may be more relevant when comparing man and mice, the dose would be 170 mg × 2 daily in a 70-kg human.[50] Mice are known to metabolize substrates at a higher rate than humans,[51] thus a lower dose could be equally efficient in humans. Healthy fasting humans given a single oral dose of 100 mg camostat mesylate reach maximal plasma levels of GBPA 0.15 μM (unpublished data). It is therefore likely that camostat mesylate doses well below 2100 mg will be sufficient in achieving relevant SARS-CoV-2 inhibitory plasma concentrations.

8 | DISCUSSION

The COVID-19 pandemic has accentuated the need for drug repurposing while awaiting the pharmaceutical development of highly potent antiviral compounds against SARS-CoV-2. So far, anti-inflammatory corticosteroids are the only available option for the vast majority of patients and healthcare professionals burdened by the pandemic, as Remdesivir accessibility is restricted. Until a specific anti-SARS-CoV-2 drug is developed, the use of compounds with favourable safety profiles is essential when attempting to reduce morbidity and mortality. SARS-CoV-2 virions stimulate the respiratory epithelium and immune cells to produce cytokines and chemokines which cause leukocyte infiltration and potential lung damage, lung oedema, and in the most severe cases compromised gas exchange.[52] Camostat mesylate has been tested on numerous patient groups with large age spans and therefore appropriately covers the diverse demography of patients suffering from COVID-19. Moreover, safety data on small groups of patients, cover a large span of doses achieving the antiviral concentrations found in human cells and mice (Table 1). A possible advantage of blocking a critical host component like TMPRSS2 using camostat mesylate, and not targeting the virus itself, is that it will be more resilient to the rapid development of viral resistance, since individual point mutations in viral components are unlikely to compensate for the loss of a critical host factor.[53] On the other hand, one of the drawbacks of a drug limiting cell entry may be the need for early treatment initiation during the first phase of the infection to minimize cell damage and cytokine production,[18] hence treatment may have to be initiated before occurrence of severe COVID-19.[54-56] The majority of antiviral studies have been done on mice and human cells pretreated with camostat mesylate.[12,30,35,57] However, in these studies, the viral challenge dose administered presumably far surpasses the viral inoculum contracted by interpersonal infection essentially providing time for the pharmacological intervention. Additionally, any reduction in inflammation in the lung, no matter the effect size, may reduce mortality. Another obvious advantage of using a serine protease inhibitor like camostat mesylate is that it is neither metabolized by nor an inhibitor of the CYP system, and thus is predicted to have very low potential for pharmacokinetic interaction with other drugs.[13] Camostat mesylate may therefore be used in combination with, for example, corticosteroids and Remdesivir to reduce cell entry, replication and inflammation. The antiviral potential of camostat mesylate has attracted significant attention, and multiple clinical trials are either actively recruiting or planned. As of September 2020, 12 clinical trials have been registered to test camostat mesylate in up to 3000 patients and some of the trials have registered more than one cohort. Eight of the trials are randomized, double or quadruple, blinded studies with clinical endpoints including viral load, hospitalization days and mortality. Eight trials are testing camostat mesylate as a monotherapy on hospitalized patients, seven trials are on outpatient cohorts and three trials are as add-on therapies in combination with other drugs. These clinical trials are running in Denmark (CamoCO-19, NCT04321096), USA (RECOVER, NCT04470544, NCT04353284, NCT04524663, NCT04374019), UK (NCT04455815), Mexico (NCT04530617), Israel (COSTA, NCT04355052), Germany (NCT04338906), South Korea (NCT04521296) and Japan (NCT04451083) and should provide valuable insight into the potential utility of camostat mesylate in treating COVID-19. A recent open-label case-control study with camostat mesylate on COVID-19 intensive care patients shows promise for these ongoing trials.[58]

In conclusion, based on human cell and animal studies, camostat mesylate is a promising repurposed drug against COVID-19 by inhibiting viral particle entry and possibly inflammation, and the drug has an excellent safety profile in humans. The results of the ongoing trials worldwide will be awaited with interest, and further trials will be necessary for investigating synergy with other anti-SARS-CoV-2 drugs.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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