#### **CORRESPONDANCE**

# What do We Know About the Serine Protease Inhibitor Camostate in SARS-CoV-2-infection?

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Received: 25 April 2022; Accepted: 16 May 2022; Published: 23 May 2022

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SARS-CoV-2 has triggered a pandemic of "coronavirus disease-2019" (COVID-19). Viral cell entry of coronaviruses relies on binding of viral spike protein (S protein) to cellular receptors and S protein processing by host cell proteases. It is known that SARS-CoV-2 uses the human receptor ACE2 for cell entry and the serine protease TMPRSS2 for "priming" of the S protein. Camostat has antiviral properties against coronaviruses. The effects are due to inhibition of the endogenous protease TMPRSS2, which the SARS-CoV-2 virus requires for host cell entry (and exit). Camostat is a serine protease inhibitor. Camostat, which is already in clinical use, reduces cell infection. So far, this has been shown exclusively in cell lines or cell cultures, which do not reflect the complexity of the three-dimensional alveolar lung cell association with type I, type II cells, endothelial cells and alveolar macrophages. It is well known, that Camostat blocks TMPRSS2 and related proteases [1-36]. For SARS-CoV-2 to enter lung cells, the virus must be activated by the cellular protease TMPRSS2. Camostat is used in Japan to treat inflammation of the pancreas, blocks the protease TMPRSS2 and thereby inhibit SARS-CoV-2 [1-18, 20-29, 31,32,34,35]. However, it was unclear whether the camostat degradation product GBPA also inhibits the virus and whether the virus can use related proteases for infection in addition to TMPRSS2, which may not be inhibited by camostat [18,20,29] These proteases are available to the virus for replication in the upper respiratory tract and are inhibited by camostat [1-36]. It is therefore not possible for SARS-CoV-2 to evade the antiviral effect of Camostat by switching to related proteases instead of TMPRSS2. In further studies, the researchers were able to show that in addition to Camostat, the primary Camostat metabolite GBPA also inhibits the protease TMPRSS2, thereby blocking SARS-CoV-2 infection. Camostat is converted to GBPA in the body within a very short time. GBPA can exert an antiviral effect in patients. A higher dosage of Camostat to effectively treat COVID-19 than to treat pancreatic inflammation may be required [33,36]. Inhibition of SARS-CoV-2 by Camostat had initially been shown only in the lung cell line Calu-3 [6]. The involvement of researchers from Hannover, Germany, made it possible to analyze the antiviral effect of Camostat in real lung tissue as well [6].

Camostat and GBPA inhibit SARS-CoV-2 infection of lung tissue [15]. The camostat mesilate-containing drug Foipan® has been available on the Japanese market since 1986 [1-36]. It is used to treat chronic inflammation of the pancreas and postoperative reflux esophagitis [33,36]. According to the product information, the substance has an inhibitory effect on several enzymes and intervenes in various systems in the body. Among other things, an inhibitory effect on trypsin and normalization of amylase levels are mentioned [33,36]. However, the reason why this substance suddenly becomes interesting in the corona crisis is different [24,26,30]. Camostat is defined 4-[[4-[(Aminoiminomethyl)amino]benzoyl]oxy]benzen-essigsäure 2-(Dimethylamino)-2-oxoethylestermethansulfonat; FOY 305; FOY-S 980; Foipan -mesylat) [1-36]. The empirical formula is C20H22N4O5.CH3S=3H [24,35]. The molecular weight is 494.52. The melting point is between 164-168 degrees. Camostat is stored in the refrigerator. The UN No. is 3077, the CAS No. is 59721-29-8. Camostat belongs to the protease inhibitor class of drugs, and its mechanism of action is antifibrinolysis [1-36]. Camostat is a synthetically produced active ingredient from the protease inhibitor group [1-36]. It is approved in Japan as Foipan (Manufacturer: Ono pharmaceutical) for the oral treatment of chronic pancreatitis and postoperative esophagitis caused by reflux of gastric acid [33,36]. Chemically, camostat is a derivative of p-aminobenzoic acid. The active ingredient is used medicinally as camostat mesilate, i.e., as the salt of methanesulfonic acid [1-36]. Camostat inhibits in vitro various pancreatic and plasmatic proteolytic enzymes such as trypsin, plasmin, pancreatic kallikrein, plasma kallikrein, and thrombin, as well as the hydrolytic activity of C1r and C1 esterase [33,36]. Camostat further inhibits the cellular protease TMPRSS2 in vitro [1-18, 20-29, 31,32, 34,35]. The efficacy of Camostat in different cell cultures has already been demonstrated [1-36]. Camostats inhibits TMPRSS2, the enzyme is expressed on the human cell surface after autocatalytic activation, mainly in the small intestine and to a lesser extent in the liver, heart, prostate, thymus and lung [1-36]. According to studies, SARS-CoV-2, the virus responsible for COVID-19, requires TMPRSS2 present in the human body to enter the host cell, which may provide a target for treatment [1-18, 20-29, 31,32, 34, 35]. Therapeutic efficacy in COVID-19 patients remains to be tested in clinical trials [2, 3, 4, 6, 24, 32]. Similarly, it is to be investigated whether the active substance can be injected directly into the lungs. It is unclear whether camostat per se is sufficiently available in the lungs. According to scientific information of the German Federal Institute for Drugs and Medical Devices, the necessary doses, extrapolated from results obtained in cell cultures, would be so strong in patients of standard weight that serious side effects could occur. Camostat is among the drugs for which the German Federal Ministry of Health initiated central procurement in April 2020 for the treatment of infected and severely ill COVID-19 patients in Germany. Since COVID-19 therapy is an individual therapeutic trial without clinical proof of efficacy, its use should be considered on a patient-by-patient basis, primarily for severe forms of the disease.

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