On the Road Back to Normalcy: Following Science Over Noise in SARS-CoV-2

The persistence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, despite the rapid development of effective vaccines, has led to the slowly emerging acceptance that eradication of COVID-19 is unlikely and that strategies for ongoing management are needed. To that end, ongoing research into disease mechanisms remains vital, and the current article by Dr Parmar reviews a key mechanism of SARS-CoV-2 infectivity with potential therapeutic significance.

The importance of transmembrane protease serine 2 (TMPRSS2) in SARS-CoV-2 was first highlighted in March 2020 by Hoffmann et al. This seemingly instantaneous elucidation of a mechanism at the beginning of the pandemic was made possible because SARS-CoV-2 shares approximately 76% of its amino acid sequence with SARS-CoV, the virus responsible for the severe acute respiratory syndrome outbreak of 2002-2003. Whereas that outbreak was successfully contained, it nevertheless led to research that elucidated the key roles of TMPRSS2 and angiotensin-converting enzyme 2 for viral entry into human cells. Hoffmann et al had the insight to quickly replicate these experiments, and they also demonstrated that the TMPRSS2 inhibitor camostat can decrease SARS-CoV-2 infectivity in cell line studies.

As Dr Parmar notes, studies of camostat and related TMPRSS2 inhibitors were rapidly launched around the world, including by our group at Mayo Clinic. Our study is testing camostat mesylate, given 4 times daily, in addition to standard of care to hospitalized patients with COVID-19 (NCT04470544). Other studies span the spectrum of disease states from early, minimally symptomatic infections to the severely ill and given in combination with a variety of different agents (Table). Early results have been mixed. A Danish study randomized 137 hospitalized patients to camostat mesylate at 200 mg 3 times daily vs placebo, with the primary outcome measure being time to discharge or clinical improvement. The investigators reported a median time to clinical improvement of 5 days in both groups (P=.31). The hazard ratio for 30-day mortality in the camostat compared with the placebo group was 0.82 (95% CI, 0.24 to 2.79; P=.75). A similar study in Japan randomized 133 asymptomatic to moderately ill patients to camostat or placebo with a primary end point of time to SARS-CoV-2 test result negativity and saw no difference. A third negative study, ACTIV-2, enrolled 224 participants in a single arm design that examined changes in viral shedding or symptomatic improvement. The announced results state that the camostat arm failed to reach the predetermined criteria for advancement and has thus been discontinued. In contrast, a South Korean study reported thus far only in a press release announced a 40% faster recovery rate for patients treated with camostat. The benefit was greater in patients older than 50 years, with a more than 50% improvement in the recovery rate. In that study, 175 patients were randomized to camostat vs placebo.

Although the hue and cry of public, media, and political demands may deem such data to be unsatisfactory, experienced scientists and investigators are all too familiar with the difficulty of scientific endeavor and discovery. Progress occurs in fits and starts or often too slowly, then all at once. Further analysis is needed to understand whether the existing data point to drug failure or flaws or limitations of study design. The results of the remaining ongoing studies should be instructive, and an international consortium of camostat

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### TABLE. Studies Involving Camostat Mesylate

| Study, PI, and country | Study design and target population | Randomization, agents, and enrollment | Outcomes analyzed | Results |
|-----------------------|-----------------------------------|--------------------------------------|------------------|---------|
| NCT04321096; EudraCT 2020-001200-42 Gunst et al<sup>7</sup> Denmark and Sweden | Multicenter, double blind, randomized, placebo controlled Hospitalized (mild, moderate, severe, and critical) | Randomization 2:1 N=205 Camostat (n=137) and placebo (n=68) Camostat mesylate 200 mg 3 times a day x 5 days or placebo | Primary outcome: time to discharge or clinical improvement (measured as ≥2 points improvement on 7-point ordinal scale) | Camostat mesylate treatment did not significantly improve clinical outcomes |
| NCT04451083 Kitagawa et al<sup>7</sup> Japan | Phase 1 study Healthy participants; pharmacokinetics and safety profiles were evaluated | Camostat mesylate orally 600 mg 4 times a day | Time of plasma GBPA concentration exceeding effective concentration was estimated as time above half-maximal effective concentration (EC<sub>50</sub>) | Camostat mesylate was safe and tolerated |
| Phase 3 study by ONOPharmaceutical<sup>8</sup> (press release) Japan | Phase 3 study, multicenter, double blind, randomized, placebo controlled Asymptomatic to moderate COVID-19 | Camostat (n=77) and placebo (n=76) Camostat mesylate orally 600 mg 4 times daily x 14 days | Primary end point: time to SARS-CoV-2 negative test result | Camostat mesylate did not meet the time to requirement of SARS-CoV-2 negative test result |
| Daewoong Pharmaceutical<sup>9</sup> (press release) South Korea | Phase 2b Placebo-controlled, randomized, and double-blind multicenter clinical trial Mild COVID-19 | N=342 Camostat=86 Placebo=89 | Primary end point: time taken to improve clinical symptoms | Improvement of symptoms such as cough and dyspnea in patients >50 years was twice as fast and statistically significant (treatment group, 4 days; placebo group, 9 days) |
| ACTIV-2 phase 2 study<sup>10</sup> | Placebo-controlled, randomized, and double-blind multicenter clinical trial | N=224 Camostat orally 200 mg every 6 hours x 7 days | Primary end point: early changes in viral shedding or improvement in symptoms | Phase 2 data failed to meet the criteria for graduation to phase 3 |
| NCT04321096; EudraCT 2020-001200-42 Søgaard et al<sup>11</sup> Denmark | Randomized, placebo controlled Mild and severe | Randomization 1:1 (ambulatory) and 2:1 (hospitalized), placebo controlled Ambulatory (2 x 200) and hospitalized (120 + 60) patients Camostat 200 mg 3 times a day x 5 days Analysis completed for the in-hospital cohort | Primary end point: ambulatory: no fever 48 h plus symptom improvement 7-point clinical scale for hospitalized patients | Ongoing |
| NCT04353284 Vinetz et al<sup>12</sup> Yale University | Randomized, placebo controlled Mild ambulatory cases | Randomization 1:1 N=2 x 57 Camostat 4 x 200 mg daily x 7 days | Primary end point: viral load (analysis in batch, including saliva test) and symptoms | Ongoing |

Continued on next page
| Study, PI, and country | Study design and target population | Randomization, agents, and enrollment | Outcomes analyzed | Results |
|------------------------|-----------------------------------|--------------------------------------|------------------|---------|
| **NCT04374019** Arnold et al<sup>13</sup> Kentucky University | Randomized multiple arms Ambulatory and hospital (not ventilated) | N=60 patients per arm Comparing with ivermectin Camostat 200 mg 3 times daily x 14 days | Primary end point: 2-point deterioration on 7-point clinical scale | Ongoing |
| **NCT04455815**: EudraCT 2020-002110-41 Dhaliwal et al<sup>14</sup> CRUK/Edinburgh University | Randomized open label Ambulatory | 1:1 randomized open label N=2 × 195 patients Comparison with standard of care Camostat 200 mg 4 times daily x 14 days | Primary end point: hospitalization requiring supplemental oxygen, time frame days 1-28 | Ongoing |
| **NCT0470544** Bryce et al<sup>15</sup> Mayo Clinic Arizona | Randomized placebo controlled Hospitalized patients | 1:1 randomized N=2 × 138 patients Camostat 200 mg 4 times daily x 14 days | Primary end point: alive and free from respiratory failure at day 28 | Ongoing |
| **NCT04435015** Mani et al<sup>16</sup> Yale University | Randomized placebo controlled Hospitalized patients | 1:1 randomized N=2 × 100 patients Camostat 200 mg 3 times daily until discharge | Primary end point: D-dimer | Ongoing planned |
| **NCT04608266** EudraCT 2020-003366-39 (CAMOVID) Boutboul et al<sup>17</sup> France | Randomized, placebo controlled Ambulatory | 1:1 randomized N=2 × 298 patients Camostat 200 mg 3 times daily x 14 days | Primary end point: hospitalization | Ongoing recruitment |
| **NCT04521296** Daewoong Pharmaceutical<sup>18</sup> South Korea | Randomized, placebo controlled, phase 2a, phase 2b Mild to moderate COVID | 1:1 randomized N=2 × 45 patients in phase 2a, 300 patients in phase 2b Camostat 200 mg 3 times daily x 14 days | Primary end point: time to negative RNA | Ongoing | Recruitment complete |
| **NCT04530617** Palazuelos et al<sup>19</sup> Mexico | Randomized, placebo controlled Ambulatory | 1:1:1:1 randomized N=4 × 90 patients Camostat 200 mg 3 times daily x 14 days | Primary end point: hospitalization and oxygen use at day 14 | Ongoing recruitment |
| **NCT04524663**: NCT04662073; NCT04662086 Parsonnet et al<sup>20</sup> Stanford | Randomized, placebo controlled (adaptive design, sharing controls) Ambulatory | 1:1 randomized N=2 × 60 patients Camostat 200 mg 4 times daily x 10 days | Primary end point: viral shedding, up to day 28 | Ongoing recruitment |

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| Study, PI, and country | Study design and target population | Randomization, agents, and enrollment | Outcomes analyzed | Results |
|------------------------|-----------------------------------|-------------------------------------|------------------|---------|
| NCT04583592 (CAMELOT) | Sagent Pharmaceuticals | Randomized, placebo controlled Ambulatory | 2:1 randomized N=200 + 100 patients Camostat 200 mg 4 times daily × 14 days | Primary end point: hospitalization or death before day 28 | Ongoing—recruitment complete |
| NCT04625114 De Scheerder et al | Belgium | Randomized, placebo controlled Mild symptoms or no symptoms with high viral load Ambulatory | 1:1 randomized N=2 × 75 patients Camostat 300 mg 3 times daily × 5-10 days | Primary end point: viral load change from day 0 to day 5 | Ongoing recruitment |
| NCT04355052 Levi et al | Israel | Randomized, open label (amended) Hospital | 2:1 randomized N=160 + 80 patients Comparison: standard of care Camostat 200 mg 3 times daily × 10 days | Primary end point: NEWS and PCR | Ongoing recruitment |
| NCT04338906; EudraCT 2020-004695-18 Feldt et al | Germany | Randomized, placebo controlled (amended) Early treatment of ambulatory/hospital | 2:2:1:1 randomized N=332 + 332 + 166 + 166 patients Comparison: (convalescent plasma); standard of care; placebo Camostat 200 mg 3 times daily × 7 days | Primary end point: progression to clinical status ≥4b WHO | Ongoing recruitment |
| JPRN-JRCTs031200113 Yasuhiro et al | Tokyo | Randomized, placebo controlled Preventive use Ambulatory | 1:1 randomized N=2 × 300 patients Camostat 5 mg in 100 mL orally 4 times daily × 56 days | Primary end point: positive antibody or PCR test | Ongoing recruitment |
| NCT04730206; EudraCT 2020-005911-27 Van den Bruel et al | Belgium | Randomized, placebo controlled Symptomatic >50 years Ambulatory | 1:1 randomized N=2 × 653 patients Compare to placebo Camostat 200 mg 4 times daily × 7 days | Primary end point: hospitalization >24 h or death before day 30 | Ongoing, not yet recruiting |
| NCT04652765 Marshall et al | Johns Hopkins, Baltimore | Randomized open label Ambulatory | 1:1:1 randomized Comparison: standard of care Camostat 600 mg 4 times daily × 7 days + bicalutamide 150 mg daily for 7 days | Primary end point: hospitalization before day 28 | Ongoing recruitment |
| NCT04518410 (ACTIV-2) Smith et al | UC San Diego | Randomized, placebo-controlled, adaptive platform trial Symptomatic, higher risk of progression to severe disease Ambulatory | 1:1 randomized N=2000 patients Compare: IV bamlanivimab, BRII-196/ BRII-198, or AZD7442; inhaled SNG001; intramuscular AZD7442 | Primary end point: duration of symptoms | Ongoing recruitment |
| Study, PI, and country | Study design and target population | Randomization, agents, and enrollment | Outcomes analyzed | Results |
|------------------------|-----------------------------------|-------------------------------------|------------------|---------|
| jRCTs031200196 Kenji et al<sup>29</sup> Japan | Randomized open label Mild severity Hospital | 1:1 randomized N=2 x 50 patients Compare to standard of care Camostat + favipiravir + inhaled ciclesonide for 10 days | Primary end point: length of hospital stay | Ongoing recruitment |
| NCT04713176 Daewoong Pharmaceutical<sup>30</sup> | Randomized open label Severe disease Hospital | 1:1 randomized N=2 x 560 patients Compare: placebo + IV remdesivir up to 5 days Camostat 200 mg 3 times daily 14 days + IV remdesivir up to 5 days | Primary end point: mortality or ECMO up to 29 days | Ongoing recruitment |
| EudraCT 2020-002233-15 Schultz-Heienbrok et al<sup>31</sup> Germany | Randomized placebo controlled Mild severity, ambulatory | N=40 patients Comparison: placebo Camostat 600 mg 4 times daily + niclosamide 2 g x 7 days | Primary end point: viral load | Ongoing recruitment |

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; GBPA, 4-(4-guanidinobenzyloxyl)pheny lacetic acid; IV, intravenous; NEWS, National Early Warning Score; PCR, polymerase chain reaction; PI, principal investigator; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.
investigators has already been convened to analyze pooled data.

One possibility is that multidrug inhibition of SARS-CoV-2 entry will ultimately be needed to provide clinically meaningful levels of benefit. Evidence supporting combinations of entry inhibitors over monotherapy already exists with various compounds, including the cathepsin inhibitors EST [(23,25) trans-epoxysuccinyl-1-leucylamindo-3-methylbutane ethyl ester] and E64d, a proprotein convertase inhibitor, and the protease furin. It may also be that the timing, dosing, or delivery of camostat or other TMPRSS2 inhibitors remains to be optimized, and variations on these parameters, such as higher dosing and aerosolized nasal delivery, are being pursued.

Ultimately, there is every reason to believe that scientific discovery such as that reviewed here by Dr Parmar will stop the endless waves of outbreaks that strain health care systems across multidimensional communities. Whether targeting of TMPRSS2 is part of that solution remains to be seen, but insights such as these into disease mechanisms are the vital signposts guiding us back to normalcy.

Sadia Z. Shah, MD, MBA
Department of Transplantation
Mayo Clinic
Jacksonville, FL

Alan H. Bryce, MD
Division of Hematology and Medical Oncology
Mayo Clinic
Phoenix, AZ

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Correspondence: Address to Alan H. Bryce, 5777 E Mayo Blvd, Phoenix, AZ 85054 (Twitter: @AlanBryce9).

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