Introduction: The outbreak of SARS-CoV-2 infection in December of 2019 initiated a global pandemic of COVID-19. Typical symptoms of viral infection such as fever, cough and fatigue are complicated by acute respiratory distress syndrome, viral pneumonia, acute kidney injury and multiple organ dysfunction. Many patients with severe COVID-19 present with coagulation abnormalities and thrombosis associated with an increased risk of death.
Methods: Several promising antiviral agents against SARS-CoV-2 have emerged that target 1) the transmembrane protease, serine 2 (TMPRSS2) required for the virus entry, or 2) the RNA-dependent RNA polymerase (RdRp) required for the virus production. The US FDA has authorized emergency use of Gilead's antiviral drug, remdesivir for the treatment of COVID-19. The inhibitors of serine protease, camostat and nafamostat block the viral entry by inhibiting TMPRSS2 in airway cells and are evaluated for treatment of COVID-19 infection in patients. Drug repositioning screens for SARS-CoV-2 antivirals have identified several promising candidates in various stages of clinical development.
Results: We recognize that many agents tested for COVID-19 or identified for future testing have physicochemical properties that could complicate their delivery and decrease their bioavailability at the site of the action. For example, remdesivir is a poorly soluble molecule that is currently administered intravenously and uses 24-fold excess of solubilizing excipient, SBEDC. The critical needs in delivery of antiviral agents for COVID-19 include: 1) improve formulation of antiviral drugs against SARS-CoV-2 and the new agents that are repurposed for COVID-19; 2) co-delivery of multiple agents targeting different critical stages of the virus life cycle and/or anti-inflammatory agents to stop COVID-19; 3) administer all of the above directly to the nasal cavity and lungs. Towards this goal we developed 1) the injectable nanoformulation of remdesivir with 20-fold less excipient than the current Gilead's format that can possibly widen the therapeutic window of this drug; 2) the lyophilizable nanocrystal format containing 97% remdesivir and 3% excipient for inhalable aerosols.
Conclusion/Implications: Given the speed of onset of the disease and the role of lung infection in initiating the host response and rapid decline in the patient health, direct delivery of the drug as inhalable and nasal formulations to upper and lower respiratory tract can impede the progress of disease and damage to the lungs. Acknowledgement: National Cancer Institute grant U54CA198999, Project 2 (AVK) and R01AI141082 (AJH). Conflict statement: AVK: DelAQUA Pharmaceuticals (co-founder, shareholder, and president); Softkemo Pharma Corp. and BendaRx Corp. (co-founder and/or director).