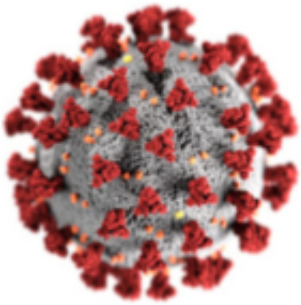

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
James Luby, M.D and Robert Haley, M.D., editors

From the Editors

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.

The Situation

In the world as of April 16, 2020, there have been 2,081,969 confirmed cases of COVID-19 with 138,147 deaths. In the United States, there have been 639,733 cases, the most in the world followed in order by Spain, Italy, Germany, France, the United Kingdom, China, Iran, Turkey and Belgium.[1] Deaths in the U.S. have been estimated at 33,940.[2] The total number of hospitalizations in the U.S. has been reported as 104,039, with New York, New Jersey, California, Michigan and Illinois being in order the first through the fifth in number. In terms of hospitalizations, Texas ranks sixteenth in the country.[1]

From March 10 through April 16 there have been 1,986 cases of COVID-19 reported from Dallas County with 43 deaths.[3] Of hospitalized cases in Dallas County, 69% have been over 60 years of age or older or have had at least one known risk condition. Diabetes mellitus was seen in 30% of all hospitalized patients. More men than women have died. Of the first cases seen in Dallas County, the distribution of cases by race/ethnicity did not differ significantly from that of the Dallas population. Differences have been seen in other cities.

References:

1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 4/16/20)
2. Worldometer. Coronavirus update 4/16/20
3. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 4/16/20

Feature Article

Remdesivir

Mamta Jain, M.D.

Remdesivir is a nucleoside analogue that acts on the RNA-dependent RNA polymerase to inhibit replication. The metabolite produced by remdesivir competes with ATP and leads to chain termination. Although coronaviruses have a proofreading mechanism to remove other nucleoside analogues, which would make the drug resistant, remdesivir appears to circumvent this mechanism. Remdesivir has broad antiviral activity and is active against SARS-CoV, MERS-CoV, Nipah, respiratory syncytial virus, Ebola, and most recently SARS-CoV-2.[1]

Remdesivir was initially used in phase II trial for the treatment of Ebola, but when compared to monoclonal antibodies (ZMapp and REGN-EB3; NCT03719586), it was found to be ineffective.[2] However, the drug administered intravenously was found to have a good safety and tolerability profile. Among the 175 patients who received the drug, there were 9 adverse events, 8 of which were considered unrelated. One patient had hypotension that was thought to be drug-related, but this was not confirmed.[3]

The first clinical case report of a patient receiving remdesivir was published in the *New England Journal of Medicine* this year. A 35 year old man who had traveled to Wuhan presented to Snohomish County, Washington with four days of fever and cough. After diagnosis of COVID-19 and with worsening respiratory symptoms requiring supplemental oxygen and pulmonary infiltrates on radiographic imaging, he was administered remdesivir on day 11 of illness and had improvement in fever and pulmonary infiltrates. He was still in the hospital at the writing of the case report.[4]

More recently, the compassionate use program at Gilead Sciences published data from 53 patients of which 30 were receiving mechanical ventilation and 4 were receiving extracorporeal membrane oxygenation. During a median of 18 days of follow-up, 17 of the 30 were extubated. Overall 47% (n=25) were discharged, and 7 (13%) died. Mortality was 18% (6 out of 34) among those on mechanical ventilation and 5% (1 out of 19) among those not on mechanical ventilation. Overall, clinical improvement was observed in 36 of 53 (68%). Adverse events were reported from 32 (60%) of the patients, the most common being liver enzyme elevation, diarrhea, rash, renal impairment and hypotension. Serious adverse events reported in 12 (23%) included multi-organ failure, septic shock, acute kidney injury and hypotension. Discontinuation of the drug occurred in 4 patients due to worsening renal impairment, maculopapular rash, and 2 for hepatic enzyme elevation.[5] Since this study did not have a comparison arm, we do not know whether these patients might have improved on their own. The data also point out adverse effects of remdesivir, such as liver enzyme elevation, that should be monitored.

At UT Southwestern, we have 2 protocols for which patients with COVID-19 can receive remdesivir. One study includes hospitalized patients with severe disease who have pulmonary infiltrates and pulse oxygenation <94% on room air or who require supplemental oxygenation or mechanical ventilation. We have enrolled 20 patients into this open-label, single-arm study. Our second study includes patients with moderately severe disease with pulmonary infiltrates and pulse oxygenation of >94% on room air; they are randomized 1:1:1 to 5 days or 10 days of remdesivir or standard of care. We have enrolled 6 patients in this study.

We anticipate that phase III placebo-controlled data will be available in the next month or so and will answer the question: does the intervention of remdesivir compared to no intervention improve clinical outcomes in hospitalized patients with severe COVID-19. The answer to this question is eagerly awaited by the global community.

References:

1. Amirian ES, Levy JK. Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. One Health 2020;9:100128.
2. Mulangu S, Dodd LE, Davey RT, Jr., et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med 2019;381:2293-303.
3. Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Med Infect Dis 2020:101647.
4. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020;382:929-36.
5. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med 2020.

Website Review

Coronavirus Resource Center

Johns Hopkins University

https://coronavirus.jhu.edu/

The Hopkins *Coronavirus Resource Center* is arguably the most useful online resource for staying abreast of the rapidly changing COVID-19 pandemic. Through a well organized, intuitive user interface it provides constantly updating statistics of confirmed cases, deaths, numbers tested, etc., globally and for individual countries, the U.S., individual states and cities. Although the numbers are obviously imperfect and subject to reporting delays and inaccuracies, given the source, these are probably the best figures available. Numbers for specific locales, such as a city, can be brought up by clicking the corresponding point on a map. Animations show trends in the growth of cases or deaths and how rapidly the "curve is being flattened." The site also provides updated news and information, basic facts on COVID-19, and videos and live events. The one slight drawback is that, since the site is so useful, it has been discovered and become so popular that click-response times have lengthened at peak times.