DASON COVID-19 Weekly Treatment Literature Update 5/29/2020
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The following summarizes key literature pertaining to treatment of COVID-19 during the past week.
*Note: some of the data discussed below is in pre-print form that has not yet been peer-reviewed. We have noted some discrepancies in some of this data, and final printed versions may ultimately differ from what is shown here. We will update as soon as possible; caution is advised when interpreting this literature.

**Remdesivir**

**Remdesivir Access:** Additional shipments continue to be distributed to state health departments. We have heard from many of you regarding your supply of remdesivir. If we can be of any assistance to you through the allocation process, please reach out to your DASON liaison.

The remdesivir summary table has been updated with the information outlined below and can be found at this link: [https://dason.medicine.duke.edu/summary-recent-clinical-data-use-remdesivir-covid-19](https://dason.medicine.duke.edu/summary-recent-clinical-data-use-remdesivir-covid-19)


These data are the preliminary results from the first stage of the Adaptive COVID-19 Treatment Trial (ACTT-1). The first arm of this trial was unblinded early by the data and safety monitoring board based on findings that showed a shortened time to recovery in patients receiving remdesivir. This randomized, double-blinded, placebo-controlled trial included 1063 patients from 60 sites and 13 subsites across 10 countries who were hospitalized between February 21, 2020 and April 19, 2020. The primary endpoint was the time to recovery, defined as discharge from the hospital or continued hospitalization only for the purpose of infection control (i.e. satisfied categories 1, 2, or 3 on the eight-category ordinal scale), with remdesivir as compared to placebo. Of note, the primary endpoint was modified by statisticians without knowledge of outcome data due to updated external knowledge indicating that COVID-19 had a longer course of illness than accounted for in the initial trial design. Secondary endpoints included mortality, change in clinical status at day 15, grade 3 and 4 adverse events, and serious adverse events. The 1:1 randomization included 1059 patients, of which 538 received remdesivir (200 mg IV on day 1, followed by 100 mg IV daily on days 2-10 or until hospital discharge or death) and 521 received a matched placebo. Randomization was stratified based on disease severity at enrollment and study site. Mean age was 58.9 years and 64.3% of patients were male. Co-existing conditions were common with 27% of patients having one condition and 52.1% having two or more and the most common pre-specified conditions included hypertension (49.6%), obesity (37%), and type 2 diabetes mellitus (29.7%). Severe disease criteria were met at enrollment for 943 (88.7%) patients. The eight-category ordinal scale ranks* at enrollment were as follows: 7-272 (25.6%); 6-197 (18.5%); 5-421 (39.6%); 4-127 (11.9%). The median days between symptom onset and randomization was 9 (IQR, 6-12). Remdesivir was superior to placebo in shortening median recovery time in hospitalized adults with COVID-19 to 11 days (95% CI, 9-12) vs. 15 days (95% CI 13-19) for placebo, (rate for recovery 1.32; 95% CI, 1.12 – 1.55; P<.001). 14-day mortality was 7.1% for remdesivir and 11.9% for placebo, but the difference was not statistically significant (HR 0.70; 95% CI, 0.47 –
Patients receiving remdesivir had higher odds of improvement in clinical status by day 15 than those receiving placebo (OR 1.5, 95% CI: 1.18-1.91).

Serious adverse events (AEs) were less common in patients randomized to remdesivir (21.1% vs. 27%). Patients randomized in the first 10 days after symptom onset had a rate ratio for recovery of 1.28 (95% CI, 1.05-1.57; 664 patients), and those randomized more than 10 days after symptom onset had ratio for recovery of 1.38 (95% CI, 1.05-1.81; 380 patients). Limitations of this study include a lack of 28-day outcomes data due to the fact that many patients had not completed 29-day follow-ups at the time of the analysis and 15-day follow-ups may not represent the full course of Covid-19. Other limitations include other missing data and baseline differences in the treatment groups: patients in the placebo arm had sicker patients than the remdesivir arm (ordinal scale score of 7* of 28.2% vs. 23.1%). The authors caution that to fully understand the efficacy of remdesivir, full statistical analysis of the entire trial population is needed. They also share that due to high mortality rates in the remdesivir arm, treatment with combination therapy may be warranted for future studies. This clinical trial is still on-going with remdesivir as the standard of care in the second stage of the study.

*Table 1. Eight-category ordinal scale used for ACTT-1 trial*

<table>
<thead>
<tr>
<th>Rank</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>not hospitalized, no limitations on activities</td>
</tr>
<tr>
<td>2</td>
<td>not hospitalized, limitation of activities, home oxygen requirement, or both</td>
</tr>
<tr>
<td>3</td>
<td>hospitalized, not requiring supplemental oxygen and no longer requiring on-going medical care (used when hospitalizations were extended for infection control purposes)</td>
</tr>
<tr>
<td>4</td>
<td>hospitalized, not requiring supplemental oxygen but requiring medical care for Covid-19 or other medical condition</td>
</tr>
<tr>
<td>5</td>
<td>hospitalized, requiring supplemental oxygen</td>
</tr>
<tr>
<td>6</td>
<td>hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices</td>
</tr>
<tr>
<td>7</td>
<td>hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)</td>
</tr>
<tr>
<td>8</td>
<td>Death</td>
</tr>
</tbody>
</table>

The supplementary appendix for the trial is currently located at this link:
Goldman JD, et. al. Remdesivir for 5 or 10 days in Patients with Severe Covid-19. NEJM. 27 May 2020. Available at: https://doi.org/10.1056/NEJMoa2015301

This randomized, open-label trial enrolled 397 patients in 55 hospitals across 8 countries from March 6 to March 26, 2020 and evaluated the primary endpoint of clinical status on day 14 as assessed on a 7-point ordinal scale (Table 2) for patients receiving 5-day vs. 10-day courses of remdesivir. Patients were stratified by demographics, but not baseline characteristics and randomized 1:1 to remdesivir 5-day or 10-day courses of therapy. The trial included hospitalized patients with oxygen saturation ≤94% on ambient air or patients receiving supplemental oxygen, radiologic evidence of pneumonia, age ≥12 years and SARS-CoV-2 established by PCR within 4 days before randomization. Patients were excluded for ALT/AST ≥5 times the upper limit of normal or CrCl < 50 ml/min or for receiving other COVID-19 therapy in the prior 24 hours, receiving ECMO or mechanical ventilation at screening, and for signs of multiorgan failure.

The trial found no significant difference in efficacy between 5-day and 10-day courses of remdesivir in patients with severe COVID-19 who do not require mechanical ventilation. At day 14, clinical improvement of ≥2 points on a 7-point ordinal scale occurred for 64% of patients receiving 5-day courses and 54% of patients on 10-day courses. Once patients were adjusted for the poorer baseline clinical status in the 10-day group, clinical status at day 14 was similar among the two groups (P=0.14), as well as time to clinical improvement, recovery, and mortality. The most common AEs noted with remdesivir include: nausea (9%), constipation (7%), elevated ALT (7%), and worsening respiratory failure (8%). There were several other limitations besides the difference in baseline severity of illness between groups. Missing data were input as the most recent assessment for missing values at day 14. Due to low numbers of patients receiving mechanical ventilation prior to treatment, these findings may not be generalizable to critically ill patients. The trial allowed for hospital discharge prior to completion of therapy; therefore, 44% of patients in the 10-day arm did not complete their full course of remdesivir. Authors caution that the magnitude of the impact of remdesivir cannot be fully evaluated due to a lack of a placebo arm. Additional studies are needed to evaluate the ideal duration of remdesivir in patients with COVID-19 who are intubated at baseline, immunocompromised, and other high risk groups. Please note, this publication represents data from the early phase of this study. The protocol was modified on April 6, 2020 to expand enrollment by 5600 patients, include a mechanical ventilation cohort and modify eligibility and outcome measures. Those results are not yet published and will further inform this work.

Table 2. Seven-point Ordinal Scale for Remdesivir 5 vs. 10 Days in Covid-19

<table>
<thead>
<tr>
<th>Rank</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>Hospitalized, receiving invasive mechanical ventilation or ECMO</td>
</tr>
<tr>
<td>3</td>
<td>Hospitalized, requiring high-flow oxygen or noninvasive ventilation</td>
</tr>
<tr>
<td>4</td>
<td>Hospitalized, requiring low-flow oxygenation</td>
</tr>
<tr>
<td>5</td>
<td>Hospitalized, not requiring supplemental oxygen, but receiving ongoing medical care (both related and unrelated to Covid-19)</td>
</tr>
<tr>
<td>6</td>
<td>Hospitalized, requiring no supplemental oxygen and no ongoing medical care (other than protocol-driven interventions for the study)</td>
</tr>
<tr>
<td>7</td>
<td>Not hospitalized</td>
</tr>
</tbody>
</table>
Hydroxychloroquine

Hydroxychloroquine Data: Please note, the summary table has also been updated and is available at this link: https://dason.medicine.duke.edu/summary-recent-clinical-data-use-hydroxychloroquine-and-chloroquine-covid-19


This was a very large multinational registry analysis of 96,032 patients with confirmed SARS-CoV-2 infection at 671 hospitals in 6 continents, hospitalized from 12/20/2019 to 4/14/2020 with outcomes of either discharge or death. Of note, the registry extracts electronic health record information to assess surgical outcomes, but captures a wide variety of data on all patients from these hospitals that was used for this analysis of COVID-19 treatment. Mean age was 53.8 years and 53.7% were male. Patients who started hydroxychloroquine (HCQ) or chloroquine (CQ), with or without a macrolide, within 48 hours of admission but not initiated while already on mechanical ventilation or receiving remdesivir were compared to those that did not receive these agents (standard of care [SOC]). Propensity score matching was used in the analysis to control for likelihood to receive the treatments. Baseline qSOFA <1 was 81% total in the treatment groups vs 83% in SOC, and oxygen saturation was <94% in 10.7% in the treatment groups vs 9.5% in SOC. In a model controlling for numerous confounding factors, each of the treatment groups was found to be associated with a higher risk of in-hospital mortality than SOC. Mortality was 9.3% in SOC, with 18% in HCQ (HR 1.335 [95% CI 1.223–1.457]), 23.8% HCQ + macrolide (HR 1.447 [95% CI 1.368–1.531]), CQ 16.4% (HR 1.365 [95% CI 1.218–1.531], CQ + macrolide 22.2% (HR 1.368 [95% CI 1.273–1.469]). In addition, after adjusting for baseline factors, each of the treatment groups was found to have an increased risk of experiencing a de-novo ventricular arrhythmia during the hospitalization. New ventricular arrhythmias were 0.3% in SOC vs 6.1% HCQ (HR 2.369 [95% CI 1.935–2.900]), HCQ + macrolide 8.1%, (HR 5.106 [95% CI 4.106–5.983), CQ 4.3% (HR 3.561 [95% CI 2.760–4.596), and CQ + macrolide 6.5% (HR 4.011 [95% CI 3.344–4.812]). There were similar findings in propensity-matched models for each treatment group vs SOC. Limitations of this study include its observational nature (outcomes assessment limited to electronic data captured in the registry), concerns about data sources/validation in this large database, non-controlled design, and potential inability to control for other unknown factors related to the treatment received. Cause of death in relation to ventricular arrhythmia or QTc prolongation was not assessed. Time to viral clearance was not reported.

There is an accompanying editorial for this study: *Chloroquine or hydroxychloroquine for COVID-19: why might they be hazardous?*

There were also a few preprints with interesting data involving hydroxychloroquine, but these articles have not been published in a peer-reviewed journal yet:


   - Uses the TriNetX health research network
   - All hospitalized US adults between 1/20/20 and 5/1/20 with COVID specific diagnosis codes (n=3618)-eliminated patients who received COVID specific therapies (did not include azithromycin or steroids)
   - HCQ group (n=1125, 799 also received azithromycin) and control (n=2247)- then conducted propensity score matching leaving two groups of 910 patients
   - Mortality and need for mechanical ventilation similar (including in subgroup of HCQ + azithromycin)
   - Assessed time to viral clearance and clinical improvement in 270 Korean patients with lab-confirmed SARA-CoV-2
   - COVID-19 patients with “moderate” disease received HCQ plus antibiotics, (n=22), lopinavir/ritonavir plus antibiotics (n=35), or conservative treatment (n = 40)
   - HCQ was associated with faster time to viral clearance and duration of hospital stay than lopinavir/ritonavir or other conservative treatment.

   - Retrospective review of 722 patients with autoimmune disorders at two tertiary-care medical centers in Spain, of which 40% were receiving HCQ maintenance therapy
   - From 2/27/2020 - 4/16/2020 there was a similar incidence of COVID-19 in patients receiving HCQ vs those that were not: HCQ patients had 5 cases (1.7%, [95% CI: 0.5%-4.0%]) vs 5 cases in those not receiving HCQ (1.2%, [95% CI: 0.4%-2.7%]) (p=0.523)

   - Meta-analysis including 3 randomized controlled trials and 8 observational studies evaluating effects of HCQ on patient outcomes
   - Overall outcomes including mortality, clinical worsening/symptom improvement, and viral clearance were not different among those who received HCQ compared to control
   - Adverse events were significantly higher with HCQ (OR: 4.1, CI: 1.42 to 11.88; p = 0.009)

**Also of note, this HCQ preprint was retracted:** Davido B, Lansaman T, Lawrence C, et al. Hydroxychloroquine plus azithromycin: a potential interest in reducing in-hospital morbidity due to COVID-19 pneumonia (HI-ZY-COVID)? Available at: https://www.medrxiv.org/content/10.1101/2020.05.05.20088757v2
Tocilizumab

There were two non-peer reviewed studies from NC hospitals on tocilizumab posted to a pre-print web server this week. There are several important limitations to these data, but we are including them in our summary as sites may hear about this data locally. We will update our summary as additional information becomes available.


This publication details outcomes of 21 patients receiving tocilizumab in a case-control, observational study at three Cone Health acute care hospitals (including one facility dedicated to COVID treatment) from March 16, 2020 through April 22, 2020. A total of 86 patients were admitted with COVID-19 infection during this time period. Tocilizumab was dosed at either a 400 mg fixed dose (14 patients) or by weight at 8 mg/kg (7 patients) for a maximum single dose of 800 mg. The primary endpoint was inpatient mortality. Timing of tocilizumab administration from hospital admission or symptom onset was not stated or assessed.

No statistically significant difference was found in baseline comorbidity burden or average SOFA scores between patients receiving tocilizumab and patients not receiving tocilizumab therapy. However, patients receiving tocilizumab did exhibit higher levels of CRP and IL-6 at initial presentation which may be indicative of cytokine storm. While the unadjusted in-hospital mortality was 14.3% for patients treated with tocilizumab and 12.3% for those who did not receive tocilizumab, the authors report a lower risk of mortality in tocilizumab treated patients in a Cox proportional hazard model adjusting for a limited number of other factors due to the small sample size (75% reduction, HR 0.25; 95% CI 0.07 – 0.90). This point estimate should be interpreted with caution, and the large confidence interval around it are representative of uncertainty that might occur with a small sample size. Of note, prescribers chose to use tocilizumab in patients displaying more severe illness at a relatively late time point in the course of disease, but it is this group of patients that was found to have a lower risk of short-term mortality. The small sample size, selection bias, and retrospective data analysis all present limitations to the findings of this study.

Rimland CA. Morgan CE, Bell GJ, et al. Clinical characteristics and early outcomes in patients with COVID-19 treated with tocilizumab at a United States academic center. Pre-print, non-peer reviewed study available at: https://www.medrxiv.org/content/10.1101/2020.05.13.20100404v1

This was a retrospective cohort study evaluating 11 patients, 9 of 11 (82%) critically ill requiring ICU admission and mechanical ventilation, treated with tocilizumab at the University of North Carolina at Chapel Hill Medical Center from March 21, 2020 through April 25, 2020. The median dose of tocilizumab administered was 7.9 mg/kg (IQR= 5.8 – 8.1) with a median time to administration of 1 day from admission and 9 days from symptom onset. The median C-reactive protein (CRP) level at baseline was 197.3 mg/L (IQR= 146.8 - 324.9 mg/L). Of note, baseline IL-6 levels were not available for all patients. Two of the six patients with IL-6 levels at baseline had low levels.

Patients were observed for a median of 17 days. CRP levels significantly decreased from a median of 211.6 mg/L before tocilizumab to 19.7 mg/L after tocilizumab (p=0.001). However, a total of 4 of 5 patients with IL-6 levels after tocilizumab had IL-6 levels above the upper limit of quantification. The following clinical outcomes were observed: 3 deaths (27%); 5 ICU admissions on mechanical ventilation (45%); 1 transfer to an acute care floor with weaning to room air (9%); and 2 home discharges (18%). There was no evidence of improvements in oxygen requirement, other markers of severe disease, or clinical outcomes in this cohort. Limitations of this analysis include its retrospective nature, lack of control group, small sample size, selection bias, and potential lack of generalizability since it is a single center experience.