Happy Columbus Day!

Today I have focused on recent publications on treatment of SARS-CoV-2 infection. The first article is the final report of the ACTT-1 Trial. Like the preliminary report, remdesivir appears to shorten time to recovery especially if started early in the course. There was no difference in mortality at 29 days and the authors comment that given high mortality despite the use of remdesivir, treatment with an antiviral drug alone may not be enough a position the Daily Briefing has suggested. The next review was the ACTT-2 preliminary results of combination Baricitinib plus remdesivir. Remdesivir plus baricitinib was associated with a 35% decrease in mortality versus lone remdesivir among patients hospitalized with COVID-19. We await a peer review publication of results. The next article is the final report on HCQ from the RECOVERY Trials. Not a big surprise: NO benefit. The next publication also from the RECOVERY series confirms an earlier smaller trial that lopinavir–ritonavir does not improve outcomes in patients infected with SARS-CoV-2. These two publications again highlight the value of using big data to prospectively perform RCTs to answer important therapeutic questions in relatively short period of time with adequate numbers powered enough to reach statistical significance. RECOVERY trials of the antibiotic azithromycin, tocilizumab, convalescent plasma, and Regeneron's monoclonal antibody cocktail REGN-CoV2 are ongoing.

Have a wonderful day

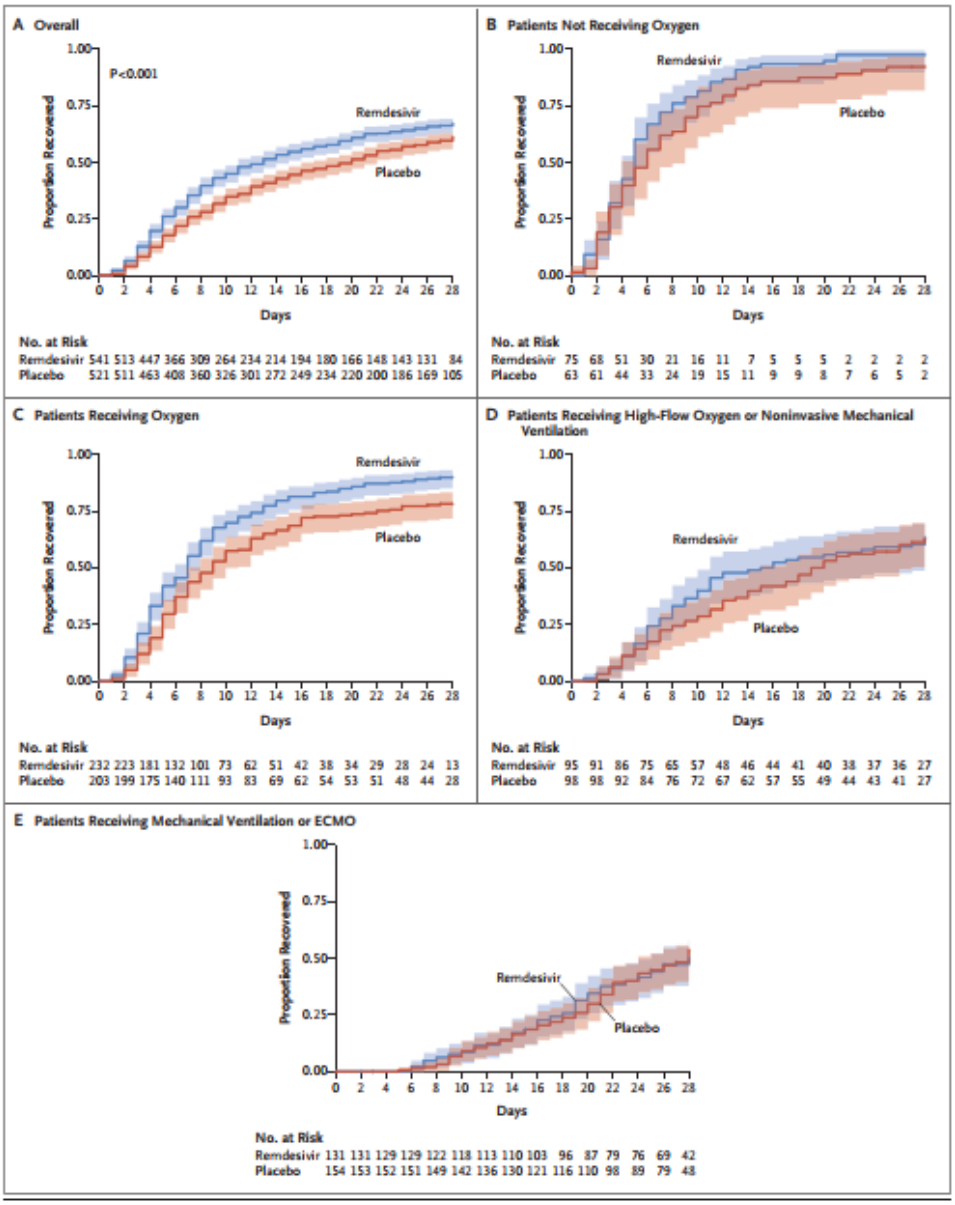
Ed

Remdesivir for the Treatment of Covid-19 — Final Report
N Engl J Med published online October 8, 2020
(ACTT-1) Study Group, randomly assigned 1,062 hospitalized COVID-19 patients with lower respiratory tract infections to receive either a placebo or remdesivir. 159 (15.0%) were categorized as having mild-to-moderate disease, and 903 (85.0%) were in the severe disease stratum. Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days, as compared with 15 days; rate ratio for recovery, 1.29; 95% confidence interval [CI], 1.12 to 1.49; P<0.001). In the severe disease stratum (957 patients) the median time to recovery was 11 days, as compared with 18 days (rate ratio for recovery, 1.31; 95% CI, 1.12 to 1.52). The rate ratio for recovery was largest among patients with a baseline ordinal score of 5 (rate ratio for recovery, 1.45; 95% CI, 1.18 to 1.79); among patients with a baseline score of 4 and those with a baseline score of 6, the rate ratio estimates for recovery were 1.29 (95% CI, 0.91 to 1.83) and 1.09 (95% CI, 0.76 to 1.57), respectively. For those receiving mechanical ventilation or ECMO at enrollment (baseline ordinal score of 7), the rate ratio for recovery was only 0.98 (95% CI, 0.70 to 1.36). Patients who underwent randomization during the first 10 days after the onset of symptoms had a rate ratio for recovery of 1.37 (95% CI, 1.14 to 1.64), whereas patients who underwent randomization more than 10 days after the onset of symptoms had a rate ratio for recovery of 1.20 (95% CI, 0.94 to 1.52). The benefit of remdesivir was larger when given earlier in the illness. The between group differences in mortality varied considerably according to baseline severity, with the largest difference seen among patients with a baseline ordinal score of 5 (hazard ratio, 0.30; 95% CI, 0.14 to 0.64).

Their overall findings were consistent with the findings of the preliminary report: a 10-day course of remdesivir was superior to placebo in the treatment of hospitalized patients with Covid-19. Patients who received remdesivir had a shorter time to recovery (the primary end point) than those who received placebo (median, 10 days vs. 15 days; rate ratio for recovery, 1.29 [95% CI, 1.12 to 1.49]) and were more likely to have improvement in the ordinal scale score at day 1 (key secondary end point;

odds ratio, 1.5; 95% CI, 1.2 to 1.9). Additional secondary end points supporting these findings include remdesivir treatment resulting in a shorter time to improvement of one and of two ordinal scale categories, a shorter time to discharge or to a sustained All-cause mortality was 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% CI, 0.52 to 1.03) at 29 days.

I think the data also suggest that treatment with remdesivir may have prevented the progression to more severe respiratory disease, as shown by the lower proportion of serious adverse events due to respiratory failure among patients in the remdesivir group, as well as a lower incidence of new oxygen use among patients who were not receiving oxygen at enrollment and a lower proportion of patients needing higher levels of respiratory support during the study. The benefit in recovery persisted when adjustment was made for glucocorticoid use, which suggests that the benefit of dexamethasone as shown in the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial may be additive to that of remdesivir.



Comment: This study confirms the greatest benefit when remdesivir is given early in patients on supplemental oxygen, but not significant if patients progress of already on high flow, MV, or ECMO at 29 days. Given high mortality despite the use of remdesivir, treatment with an antiviral drug alone may not be enough. A variety of therapeutic approaches including novel antivirals, modifiers of the immune response or other intrinsic pathways, and combination approaches are needed to continue to improve outcomes in patients with Covid-19. Current strategies are evaluating remdesivir in combination with modifiers of the immune response (e.g., the Janus kinase [JAK] inhibitor baricitinib in ACTT-2, and interferon beta-1a in ACTT-3-see below

ACTT-2: Preliminary results Baricitinib plus remdesivir

Baricitinib inhibits JAK enzymes which mediates signally of proinflammatory cytokines including IL-6. The proposed effectiveness is based on baricitinib mitigating the effects of cytokine release to limit lung damage.

Remdesivir plus baricitinib was associated with a 35% decrease in mortality versus lone remdesivir among patients hospitalized with COVID-19, according to new ACTT-2 trial findings shared within hours of final ACTT-1 results just published in the NEJM. See above

Baricitinib (Olumiant) is a JAK-1 and -2 inhibitor generally associated with the treatment of rheumatoid arthritis. Its inflammation-targeting mechanism of action led to its assessment in combined use with antiviral therapy for patients severely ill with COVID-19.

These results were presented by NIAID on the newest data from ACTT-2 at the International Society for Influenza and other Respiratory Virus Diseases Antiviral Group Virtual Conference last week. They shared clinical outcomes indicating patients who required supplemental oxygen and those who required high-flow oxygen/non-invasive ventilation at baseline—a '5' and '6' on the seven-point clinical ordinal scale used to assess COVID-19 hospitalization status—experienced the most significant improvements and reduced risks in mortality.

The NIAID investigators previously reported that baricitinib plus remdesivir achieved the ACTT-2 primary endpoint of median time to recovery: a one-day, or 12.5% overall, improvement versus lone remdesivir (8 vs 7; incidence rate ratio [IRR], 1.16; 95% CI, 1.01-1.32; *P* = .04). Recovery was defined hospital discharge or removal from supplemental oxygen during hospital care at day 29.

In the newest data, investigators observed a 35% decrease in death among patients treated with baricitinib plus remdesivir (5.1%) versus lone remdesivir (7.8%) at day 29 (hazard ratio [HR], 0.65; 95% CI, 0.39-1.08; *P* = .09). As previously noted, patients receiving oxygen at baseline reported more pronounced reductions in mortality: group 5 and group 6 patients reported 60% and 43% reduced mortality risks, respectively. It appears patients who require oxygen including high flow had the greatest benefit. No mention of steroids in this news release

Investigators reported no new safety signals among patients with COVID-19 to have received baricitinib. The team is currently working toward having complete analyses and a peer-reviewed manuscript published in the near future.

Commentary: The Daily Briefing has suggested that combination therapy with agents like IL-1, IL-6, and JAK inhibitors may improve outcomes especially in patients evolving into the inflammatory stage. Early interventions with antivirals, anti-inflammatories, and/or monoclonal/plasma appear to improve outcomes. We await additional peer reviewed robust clinical trials.

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

N Engl J Med published online October 8, 2020

This study was published on the same day as the above remdesivir study in the NEJM. This study was conducted by the UK Randomized Evaluation of COVID-19 Therapy (RECOVERY) Collaborative Group, which compared hydroxychloroquine with usual care in 1,561 hospitalized adults with SARS-CoV-2 infection. Participant enrollment began on Mar 25 and closed on Jun 5 after a preliminary analysis showed that hydroxychloroquine was ineffective.

Of the 1,561 patients randomly assigned to receive hydroxychloroquine, 421 (27.0%) died within 28 days, compared with 790 of the 3,155 patients (25.0%) assigned to usual care (rate ratio, 1.09). The authors said the study findings suggest that patients receiving hydroxychloroquine were less likely than those in the placebo group to be released from the hospital within 28 days (59.6% vs 62.9%; rate ratio, 0.90). Of patients not receiving mechanical ventilation at study enrollment, more patients who received hydroxychloroquine advanced to needing mechanical ventilation or dying than those who received usual care (30.7% vs 26.9%; risk ratio, 1.14). The rate of deaths due to cardiac events occurred in just 0.4 percentage points more patients in the hydroxychloroquine group than in the usual care group, but there was no difference between the two groups in incidence of new major heart rhythm abnormalities.

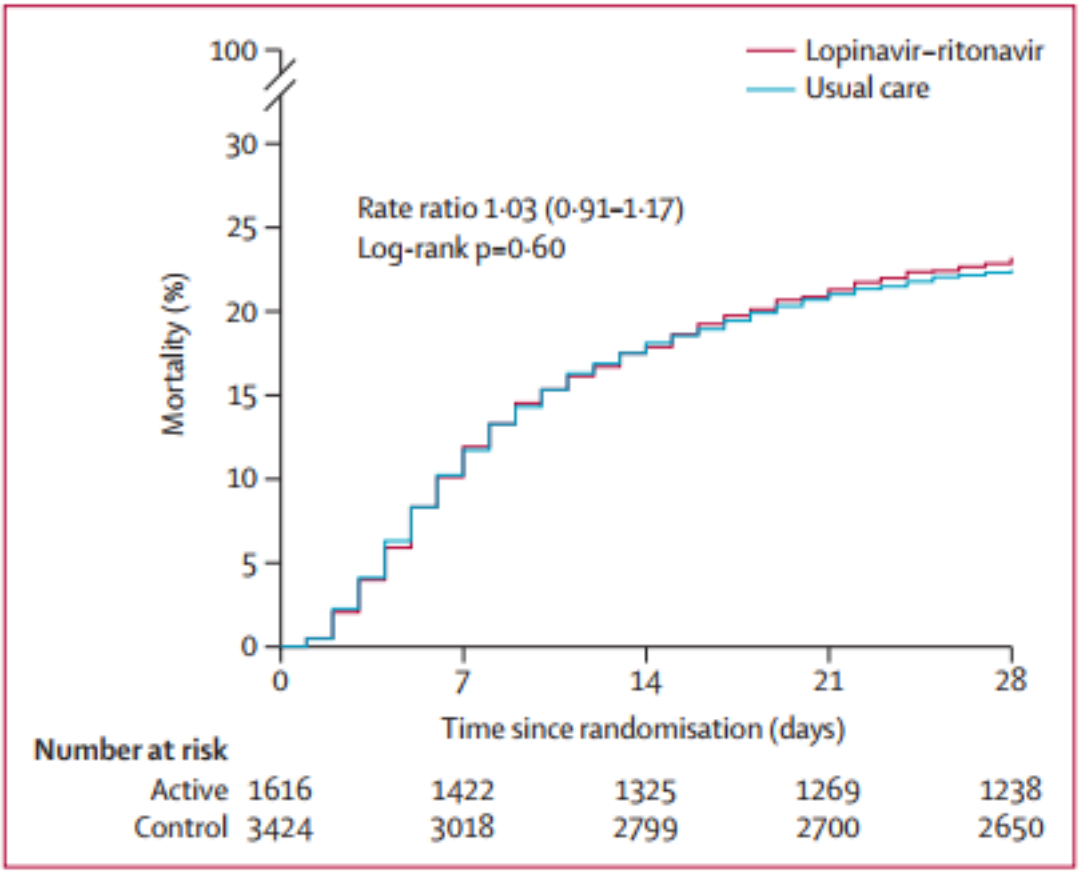
Comment: The authors concluded that hydroxychloroquine is not an effective treatment for hospitalized COVID-19 patients and that it could result in longer hospital stays and a higher risk of mechanical ventilation than usual care. Previous studies have produced mixed results, with most finding no benefit from hydroxychloroquine. The hydroxychloroquine treatment arm, along with and lopinavir-ritonavir arms, were stopped early after showing no benefit.

Lopinavir–Ritonavir in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial

Lancet published online October 5, 2020

This is another in the series of randomized, controlled, open-label, platform trial, to examine a range of possible treatments was compared with usual care in patients admitted to hospital with COVID-19. The trial is underway at 176 hospitals in the UK. Eligible and consenting patients were randomly allocated to either usual standard of care alone or usual standard of care plus lopinavir–ritonavir (400 mg and 100 mg, respectively) by mouth for 10 days or until. Randomization to usual care was twice that of any of the active treatment groups (e.g., 2:1 in favor of usual care if the patient was eligible for only one active group, 2:1:1 if the patient was eligible for two active groups). The primary outcome was 28-day all-cause mortality. Analyses were done on an intention-to-treat basis in all randomly assigned participants.

1616 patients were randomly allocated to receive lopinavir–ritonavir and 3424 patients to receive usual care. They reported no significant difference in time until discharge alive from hospital (median 11 days [IQR 5 to >28] in both groups) or the proportion of patients discharged from hospital alive within 28 days (rate ratio 0·98, 95% CI 0·91–1·05; p=0·53). Among patients not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion who met the composite endpoint of invasive mechanical ventilation or death (risk ratio 1·09, 95% CI 0·99–1·20; p=0·092).



Comment: A previous randomized trial of lopinavir–ritonavir among 199 patients admitted to hospital with COVID-19 showed no improvement in viral load, duration of hospital stay, or mortality. [reviewed in Daily Briefing months ago: NEJM 2020; 382: 1787–99]. However, the trial was felt to be too small to rule out the possibility of clinically relevant benefits and reviewers recommended larger randomized trials to confirm or refute the lack of effect. The finding of no clinical benefit from lopinavir–ritonavir treatment compared with standard care supports earlier findings published in the NEJM article.
Trials of the antibiotic azithromycin, tocilizumab, convalescent plasma, and Regeneron's monoclonal antibody cocktail REGN-CoV2 are ongoing.