UAMS Journal Club Summary
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COVID-19 Therapies: Remdesivir Compared to Placebo

Clinical Bottom Line

There is no statistically significant benefit to treating patients with severe covid-19 with remdesivir, but one study was stopped early before achieving target sample size and was therefore underpowered, and the other study (Grien et al) was unblinded without a control group. More, higher quality evidence is needed to determine the role of remdesivir in the treatment of severe COVID-19.

Of note, an additional higher quality study was published shortly after this journal club showing reduction in time to clinical improvement by 4 days, making it a more viable treatment option for COVID patients.

PICO Question

P - Patients age 18 or over with severe COVID-19
I - 10 day course of IV remdesivir (200 mg on day 1, 100 mg qd d2-10)
C - Placebo infusion of the same volume and duration
O - Clinical improvement

Background

The novel coronavirus, SARS-CoV-2, and its associated illness, COVID-19, have placed a significant burden on--and in some cases, overwhelmed---healthcare systems around the world.

As of the publication of this article, no specific antiviral drug has been proven effective in treating patients with COVID-19. Remdesivir (GS-5734) is a nucleoside (adenosine) analogue prodrug manufactured by Gilead Sciences. It was originally developed to treat hepatitis C and was trialed as a treatment of Ebola virus but was unsuccessful. The mechanism is “chain termination” via inhibition of RNA polymerase.

Remdesivir has been shown to inhibit human and animal coronaviruses, including SARS-CoV-2, in vitro. It has also been shown to inhibit replication of SARS-CoV-1 and SARS-CoV-2 in vivo in animal models.

Trial 1

Weng et al *Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.* The Lancet, Volume 395, ISSUE 10236, P1569-1578, May 16, 2020

Link: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

Validity Rating: Low risk of bias, except that trial was stopped early.

Funded by Chinese government

The Basics:
This article is a multicenter, double-blinded RCT conducted over 10 hospitals in Wuhan, Hubei, China. Patients were randomized in a 2:1 ratio to a 10 day course of IV remdesivir (200 mg on day 1, 100 mg qd d2-10) or a 10 day course of IV placebo of the same volume.

On days 0 through 28, patients were assessed on a six category ordinary scale: 1 = discharge or meeting discharge criteria (clinical recovery*); 2 = admitted but no supplemental O2 requirement; 3 = O2 therapy but not requiring high-flow or NIV; 4 = high-flow or NIV; 5 = mechanical ventilation or ECMO; 6 = death.

*Clinical recovery = normalization of pyrexia, RR <24 bpm, peripheral O2 sat >94% on RA, relief of cough, all maintained x72 hours minimum.

Inclusion Criteria:
- Men and nonpregnant women 18 years of age or older
- RT-PCR positive for SARS-CoV-2
- Radiographically confirmed pneumonia
- O2 sat 94% or less or RA, or PaO2/FiO2 300 or less
- And within 12 days or less of symptom onset

Exclusion Criteria:
- Pregnancy or breastfeeding
- Hepatic cirrhosis
- AST or ALT over 5x upper limit of normal
- Known GFR <30 or CRRT/HD/PD
- Possibility of transfer to a non-study hospital with 72 hrs
- Enrolment into an investigational treatment study for COVID-19 in past 30 days

Primary Outcomes:
Time to clinical improvement within 28 days of randomization, defined as a two-point reduction in patient's admission status on a six-point ordinal scale or live discharge from hospital, whichever came first.

Secondary Outcomes:
- Proportion of patients in each category of the six-point scale at day 7, 14, and 28 after randomization
- All cause mortality at day 28
- Frequency of mechanical ventilation
- Duration of oxygen therapy
- Duration of hospital admission
- Proportion of patients with nosocomial infection

Results:
237 patients enrolled: 158 assigned to remdesivir group and 79 to placebo group, but 3 patients in treatment group did not start treatment and 1 patient in placebo group withdrew consent. 155 patients received remdesivir, 5 for fewer than 5 days = 150 in per-protocol population. 78 patients received placebo, 2 for fewer than 5 days = 76 in per-protocol population.

At day 29, remdesivir was not associated with a difference in time to clinical improvement.

- Proportion of patients in each category of the six-point scale at day 7, 14, and 28 after randomization – not significantly different
- All cause mortality at day 28 - similar
- Frequency of mechanical ventilation - no different in duration of ventilation
- Duration of oxygen therapy - no difference
- Duration of hospital admission - no difference

Limitations/Bias:
Study was terminated early before attaining specified sample size "because the outbreak of COVID-19 was brought under control in China." Target sample size was 325 total pts across both groups to achieve 80% power under one sided type-1 error. With number enrolled power was reduced to 58%.
Use of other treatments (lopinavir-ritonavir, interferon, steroids) was permitted

Trial 2

Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19 [published online ahead of print, 2020 Apr 10]. *N Engl J Med*. 2020;NEJMoa2007016. doi:10.1056/NEJMoa2007016

https://www.nejm.org/doi/full/10.1056/NEJMc2015312?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

Validity Rating: High risk of bias due to no control group and funded by Gilead Sciences (manufacturer of remdesivir).

The Basics:

Open label, observational cohort study conducted at sites across the United States (almost half of the patients), Japan, Italy, France, Germany and one patient from each of the following countries: Austria, Spain, Nederlands, Canada. Clinicians requested inclusion in study and patients were chosen based on criteria available to Gilead Sciences. Selected patients were given 200mg remdesivir IV on day 1 followed by 100mg IV for 9 more days for a treatment duration of 10 days. Clinical as well as laboratory data were collected during the treatment course, and clinical data were collected after treatment course up to discharge, death or 28 days. Primary endpoint was improvement defined by hospital discharge, improvement in ordinal scale for oxygen requirement (specifics of scale included in paper), or both.

Inclusion Criteria:

-Hospitalized with RT-PCR confirmed SARS CoV-2 infection
-94% SpO2 on RA or "need for oxygen support"

Exclusion Criteria:

-Cr clearance <30ml/min
-AST/ALT > 5X upper limit of normal
-Other investigational therapy

Primary Outcomes:

Clinical improvement defined by hospital discharge, improvement in ordinal scale for oxygen requirement (specifics of scale included in paper), or both.

Secondary Outcomes:

No true secondary outcomes, but data on death, major and minor adverse events were collected.

Results:

53 patients were included in the final analysis, 40 receiving the full 10-day course of remdesivir. 68% of patients showed clinical improvement within 18 days of the first dose of remdesivir, 84% within 28 days and 47% were discharged within the 28-day observation period. Mortality rate for patients who completed the 10-day course of remdesivir was 13% and the rate of serious adverse events was 23%, which included multi-organ dysfunction, septic shock, acute kidney injury and hypotension.

Limitations/Bias:

-Selection criteria for patients in this study were not publicized and were likely not standardized nor consistent.
-Remdesivir therapy started on average at day 11-12 of symptoms, likely after the natural course of disease has begun improvement.
-Complete absence of control group was unexplained and confounds interpretation of results

-Very small sample size despite abundance of patients with SARS CoV-2 infection at the time of this study.
-Longer follow-up time would have been ideal

Additionally:
An RCT studying remdesivir sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) was stopped early due to what they believed was proof of clinical efficacy. Some details about this preliminary release (which was released after our journal club):

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med.* 2020 May 22:NEJMoa2007764. doi: 10.1056/NEJMoa2007764. Epub ahead of print. PMID: 32445440; PMCID: PMC7262788.

https://www.nejm.org/doi/full/10.1056/NEJMoa2007764?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

-Performed at sites across the US, Mexico, Europe, Korea, Japan and Singapore.
-Primary endpoint was time from treatment initiation to “improvement” to a point suitable for discharge (even if the patient was kept in the hospital for infection control reasons). Mortality and adverse events were among the secondary endpoints.
-Study was conducted as a double-blinded RCT. Randomization was stratified by study site and disease severity.
-Pts were given either placebo or 200mg IV remdesivir day one followed by 100mg IV remdesivir day 2-10. Pts were followed through day 29.
-Total of 1063 patients were included (541 remdesivir, 522 placebo), 731 completed the study (391, 340), 301 were completing study at time of information release (132, 169).
-The result felt to be significant was a difference in median time to recovery of 11 in the remdesivir vs 15 in the placebo group with a positive rate ratio for recovery with calculated *p* value of <0.001. There was no statistically significant difference in mortality or other outcomes.
-According to this publication the groups were then unblinded but the patients were to complete the studies. It remains to be seen how many patients have remained in their original groups, but blinding has been eliminated, weakening the validity of any published results.
-A few positive points about the study include: 1. Blinded study with good study design; 2. Sponsored by NIAID instead of Big Pharma.
-Limitations include that the trial was stopped early.