Journal Club

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Journal Club

Zeynep Uzumcu
June 11, 2020

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Outline

- Review coronavirus life-cycle
- Review mechanism of action of remdesivir
- Review previous research on remdesivir
  - Wang et al
  - Beigel et al
- Close reading of article
  - Methods
  - Results
  - Discussion
- Future research
- Implications for our practice
Viral Life-cycle

- Targets respiratory and GI tract
- Interaction of spike protein and ACE-2 receptor
- Genome translation
- Protein cleavage
- Translation and RNA replication (RdRp)
- Packaging and virion release
Mechanism of action

- Prodrug - nucleoside analogue (adenosine)
- RNA chain incorporation
- Delayed chain termination
- Both *in vitro* and *in vivo* antiviral activity
- SARS, Ebola virus, MERS
Background research

- April 29, 2020 in *Lancet*
- First multicenter, randomized, double-blind, placebo-controlled superiority trial of remdesivir in COVID
- Population: 237 adults hospitalized with RT-PCR-confirmed SARS COV2 at 10 hospitals in Wuhan, China were included; 158 received RDV, 79 received placebo
- Intervention: RDV 200 mg IV on day 1 + 100 mg IV daily x9 days (10 days total) + usual care
- Control: Placebo (10 days total) + usual care
Wang et al

- The study was stopped early due to poor recruitment after including 237 patients.
- The primary endpoint was time to clinical improvement.
- There was no statistically significant difference in this endpoint, but possible small reduction in time (21 vs. 23 days).
- Lack of an observable effect could be caused by:
  - Delayed administration (median duration of illness prior to administration = 10 days)
  - Underpowering
Background research

- May 22, 2020 in NEJM
- Randomized, double-blind, placebo controlled trial testing efficacy of IV remdesivir for hospitalized adults with COVID-19.
- 1063 patients were randomized
- Treatment arm: 10 days IV remdesivir (Day 1: 200mg, followed by 9 days 100mg)
- Patients with renal failure excluded and no GFR cutoff given!
- Primary endpoint switched mid-trial from clinical improvement to time to recovery
Beigel et al

- Primary outcome: time to clinical recovery
  - Remdesivir group recovered in 11 days compared to 15 days in the control group
  - Improvement was greatest in a subgroup analysis of less ill patients
  - No benefit among patients on high-flow oxygen, noninvasive ventilation, or invasive ventilation
- Among secondary endpoints:
  - No mortality benefit
- EMCrit.org: Reduction in hospitalization duration versus increased admission of borderline patients to receive IV therapy
Summary of background research

Wang et al suggests that remdesivir accelerates recovery by 2 days on average. Beigel et al suggests 4 days to recovery.

It remains unclear whether remdesivir might affect long-term outcomes.

Patients with renal failure were excluded from ACTT-1 trial.

Implications for how healthcare system interacts with these patients (perceived availability of a therapy could increase those who seek tests...admissions for IV remdesivir?)
Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Study question

Does treatment with intravenous remdesivir for 10 days compared to 5 days in patients hospitalized with coronavirus disease 2019 (COVID-19) improve clinical status at day 14 of hospitalization?
Methods

- Randomized
- Open-label
- Phase 3 trial
- N=397 patients (200 in 5 day, 197 in 10 day)
- 55 hospitals in the United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan
- March 6 - March 26, 2020
- 200 mg of remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent 4 or 9 days.
- Both treatment groups continued supportive therapy at the discretion of the investigator throughout the duration of the trial
Inclusion and exclusion criteria

Inclusion criteria
- Oxygen saturation 94% or lower on room air
- Radiologic evidence of pneumonia
- PCR assay within four days of randomization
- Age >11 years old
- Women included only if not pregnant

Exclusion criteria
- Intubation at screening
- ECMO at screening
- Patients with signs of multiorgan failure
- (ALT) or aspartate aminotransferase (AST) levels greater than 5 times the ULN
- **Estimated creatinine clearance of less than 50 ml/min**
- Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against Covid-19 were excluded.
Patient Characteristics

10-day group was sicker:
- 13 patients developed need for ECMO or MV between screening and treatment
- 4 of these patients (2%) were assigned to a 5-day course of remdesivir and 9 (5%) to a 10-day course.
- High-flow oxygen support was required at baseline by more patients in the 10-day group than in the 5-day group (30% vs. 24%)
- Difference was statistically significant (P = 0.02).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5-Day Group (N = 200)</th>
<th>10-Day Group (N = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) — yr</td>
<td>61 (50-69)</td>
<td>62 (50-71)</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>120 (60)</td>
<td>133 (68)</td>
</tr>
<tr>
<td>Race — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>142/200 (71)</td>
<td>134/192 (70)</td>
</tr>
<tr>
<td>Black</td>
<td>21/200 (10)</td>
<td>23/192 (12)</td>
</tr>
<tr>
<td>Asian</td>
<td>20/200 (10)</td>
<td>25/192 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>17/200 (8)</td>
<td>10/192 (5)</td>
</tr>
<tr>
<td>Median body-mass index (IQR)</td>
<td>29 (25-34)</td>
<td>29 (25-33)</td>
</tr>
<tr>
<td>Coexisting conditions of interest — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>47 (24)</td>
<td>43 (22)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40 (20)</td>
<td>49 (25)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>100 (50)</td>
<td>98 (50)</td>
</tr>
<tr>
<td>Asthma</td>
<td>27 (14)</td>
<td>22 (11)</td>
</tr>
<tr>
<td>Clinical status on the 7-point ordinal scale — no. (%)</td>
<td>4 (2)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>2: Receiving invasive mechanical ventilation or ECMO</td>
<td>4 (2)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>3: Receiving noninvasive ventilation or high-flow oxygen</td>
<td>49 (24)</td>
<td>60 (30)</td>
</tr>
<tr>
<td>4: Receiving low-flow supplemental oxygen</td>
<td>113 (56)</td>
<td>107 (54)</td>
</tr>
<tr>
<td>5: Not receiving supplemental oxygen but requiring medical care</td>
<td>34 (17)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Median duration of hospitalization before first dose of remdesivir (IQR) — days</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Median duration of symptoms before first dose of remdesivir (IQR) — days</td>
<td>8 (5–11)</td>
<td>9 (6–12)</td>
</tr>
<tr>
<td>Median AST level (IQR) — UL/liter</td>
<td>41 (29–58)</td>
<td>46 (34–67)</td>
</tr>
<tr>
<td>Median ALT level (IQR) — UL/liter</td>
<td>32 (22–50)</td>
<td>36 (23–58)</td>
</tr>
<tr>
<td>Median creatinine clearance by Cockcroft–Gault (IQR) — ml/min</td>
<td>106 (80–142)</td>
<td>103 (80–140)</td>
</tr>
</tbody>
</table>

* Percentages may not total 100 because of rounding. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range. Race was reported by the patients. The body-mass index is the weight in kilograms divided by the square of the height in meters. P = 0.02 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test. P = 0.008 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test.
Primary endpoint

*Original* primary endpoint of the study was normalization of temperature and oxygen saturation through day 14.

This was changed to *assessment of clinical status* using a 7-point ordinal scale on March 15, with clinical status values collected from day 1 to 14, or until discharge.

1) death
2) hospitalized, receiving invasive mechanical ventilation or ECMO
3) hospitalized, receiving noninvasive ventilation or high-flow oxygen devices
4) hospitalized, requiring low-flow supplemental oxygen
5) hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to Covid-19)
6) hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration)
7) not hospitalized
Secondary and exploratory endpoints

**Secondary**
Proportion of patients with adverse events that occurred on or after the first dose of remdesivir for up to 30 days after the last dose.

**Exploratory**
- **Time to clinical improvement** (defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale)
- **Time to recovery** (defined by the National Institute of Allergy and Infectious Diseases [NIAID] as an improvement from a baseline score of 2 to 5 to a score of 6 or 7)
- **Time to modified recovery** (defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7)
- Death from any cause.
Results:
Clinical improvement

By day 14, clinical improvement of 2 points or more on the ordinal scale:

- 64% of patients in the 5-day group
- 54% in the 10-day group.

After adjustment for baseline clinical status, 10-day group had distribution in clinical status at day 14 that was similar to that among patients in the 5-day group (P=0.14).
Time to recovery

The median time to recovery:
- 10 days among patients in the 5-day group
- 11 days among patients in the 10-day group.

Time to modified recovery:
- 9 days among patients in the 5-day group
- 10 days among patients in the 10-day group.
Results:

Length of stay, mortality

Median duration of hospitalization among patients discharged on or before day 14 was slightly shorter for the 5-day group.

More patients were discharged from the hospital in the 5-day group than in the 10-day group.

Mortality was numerically lower in the 5-day group.

Discharge rates higher among patients who had had symptoms for less than 10 days before receiving the first dose of remdesivir (62%) than among those who had had symptoms for 10 or more days before receiving the first dose (49%).

<table>
<thead>
<tr>
<th>Measures</th>
<th>5 day tx</th>
<th>10 day tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of hospitalization</td>
<td>7 days</td>
<td>8 days</td>
</tr>
<tr>
<td>Percent discharged</td>
<td>60%</td>
<td>52%</td>
</tr>
<tr>
<td>Mortality</td>
<td>8%</td>
<td>11%</td>
</tr>
</tbody>
</table>
**Posthoc analysis**

Purpose: determine whether any subpopulation might have benefitted from receiving more than 5 days of therapy

Of patients on invasive mechanical ventilation, those treated with 10 days of remdesivir had lower mortality (7/41 vs. 10/25, p=0.048)

However: these subgroups were generated based on clinical status on day #5 – five days after patients had started therapy

<table>
<thead>
<tr>
<th></th>
<th>Invasive Mechanical Ventilation</th>
<th>High-Flow Oxygen</th>
<th>Low-Flow Oxygen</th>
<th>Ambient Air</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Day group (N=25)</td>
<td>8</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>10-Day group (N=41)</td>
<td>12</td>
<td>23</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>5-Day group (N=40)</td>
<td>28</td>
<td>20</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>10-Day group (N=35)</td>
<td>26</td>
<td>12</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>5-Day group (N=68)</td>
<td>83</td>
<td>8</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>10-Day group (N=62)</td>
<td>82</td>
<td>11</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>5-Day group (N=37)</td>
<td>79</td>
<td>15</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>10-Day group (N=22)</td>
<td>77</td>
<td>23</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>
Safety

Adverse events:
- 70% in 5 day group
- 74% in 10 day group

Serious adverse events:
- 21% in 5 day group
- 35% in 10 day group

Percentage of patients who discontinued treatment owing to adverse events: 4% vs 10%

https://emcrit.org/pulmcrit/remdesivir-5-10/
Safety

Laboratory abnormalities of grade 3: 27% vs 34%

Most abnormalities were transient, with no significant difference between the median changes in the two groups at day 14.

Grade 4 creatinine clearance reductions:
- 3% vs 12%
- 71% of these pts: MV, NIPPV, HFNC at baseline

https://emcrit.org/pulmcrit/remdesivir-5-10/
Conclusions

In patients with severe Covid-19 without mechanical ventilation requirement:

- No significant difference between a 5-day course and a 10-day course of remdesivir
- Specifically in disease severity, time to recovery, length of stay

There are significant nephrotoxic events noted in 10 day group
**Discussion**

The 10-day group included a significantly higher percentage of patients in the most severe disease categories:

- Those requiring invasive mechanical ventilation and high-flow oxygen
- Higher proportion of men (68%, vs. 60%), who are known to have worse outcomes with Covid-19

“Though results suggest that longer treatment with remdesivir may be detrimental, the trend toward improved outcomes in the 5-day group was already evident at day 5 of the trial — when both groups had received the same amount of treatment — which suggests that differences between the groups were not due to treatment duration but to observed imbalances in baseline characteristics between the two groups.”

Prior RCTs on remdesivir in COVID-19 have not reported increased rates of renal failure.
Limitations

- Funded, designed, monitored and written by Gilead
- Lack of placebo controlled group
- Open label
- Size
- Demographics
- Exclusion criteria (renal function)
- Baseline differences between 5 and 10 day groups
Future research directions

- Study of patients who require mechanical ventilation- might this group benefit from 10 days of remdesivir treatment
- Specific trials of high risk groups, such as immunocompromised persons
- Further placebo-controlled trials
Summary & Practice implications

- No placebo control => not a test of the efficacy of remdesivir
- If used, remdesivir use should be limited to 5 days
- Supplies that are likely to be limited can be conserved with shorter durations of therapy
- Potentially shorter hospital stays
- Currently not studied in patients with impaired renal function
Thanks!
References

Richard T. Eastman, Jacob S. Roth, Kyle R. Brimacombe, Anton Simeonov, Min Shen, Samarjit Patnaik, and Matthew D. Hall. ACS Central Science 2020 6 (5), 672-683. DOI: 10.1021/acscentsci.0c00489


https://emcrit.org/pulmcrit/wang-remdesivir/

https://emcrit.org/pulmcrit/actt-remdesivir/


https://emcrit.org/pulmcrit/remdesivir-5-10/