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Journal Club

Zeynep Uzumcu, MD
Thomas Jefferson University

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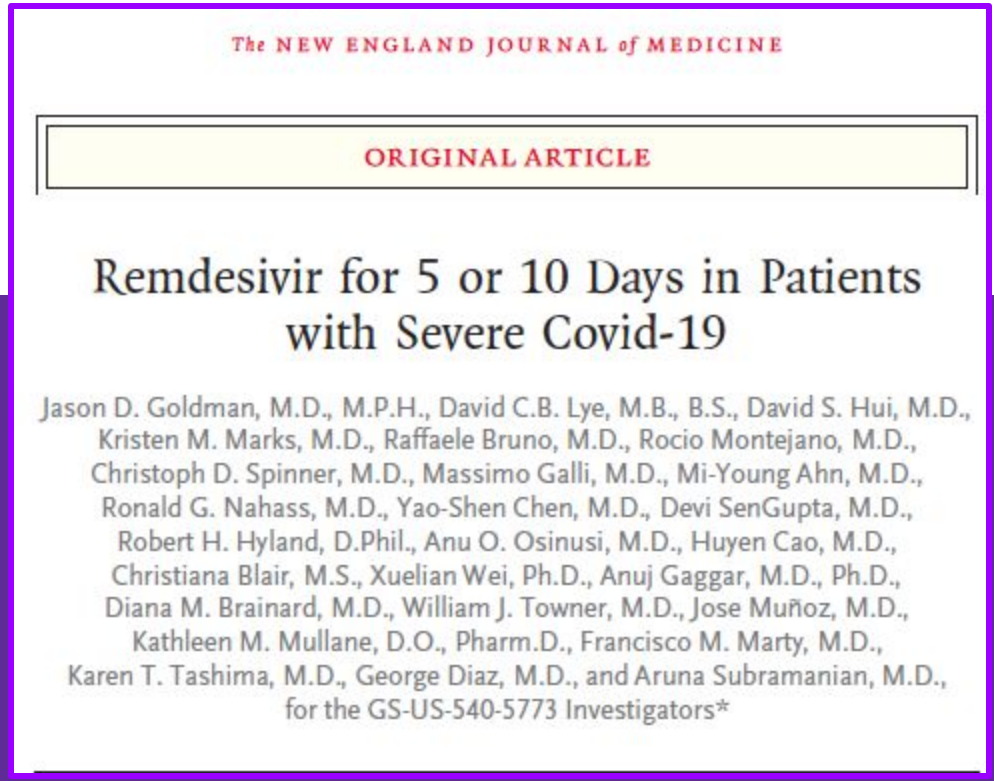
June 11, 2020

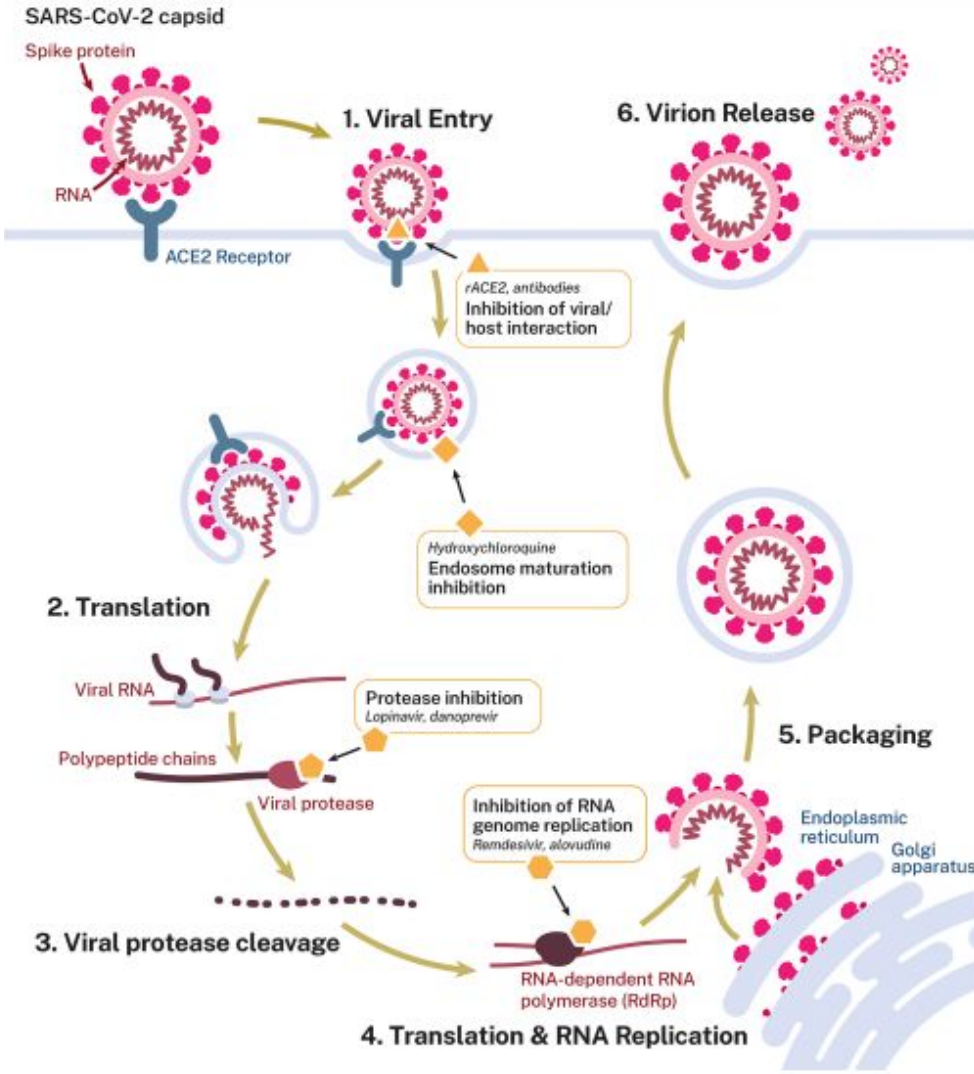


Outline

- 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

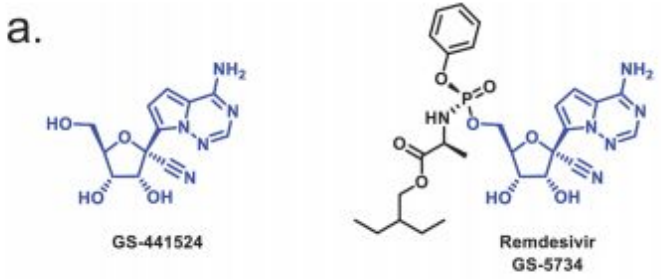
Viral Life-cycle

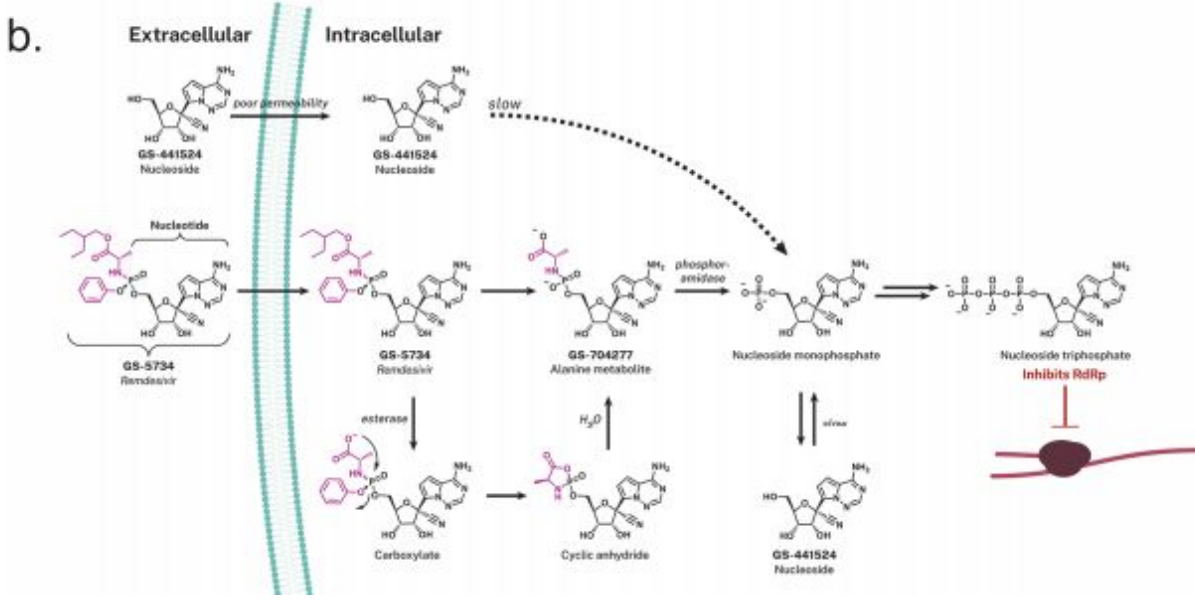
- Targets respiratory and GI tract
- Interaction of spike protein and ACE-2 receptor
- Genome translation
- Protein cleavage
- Translation and RNA replication (RdRp)
- Packaging and virion release



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

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

- 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

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

The CurbsiderS

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?)

Journal club article

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., Kristen M. Marks, M.D., Raffaele Bruno, M.D., Rocio Montejano, M.D., Christoph D. Spinner, M.D., Massimo Galli, M.D., Mi-Young Ahn, M.D., Ronald G. Nahass, M.D., Yao-Shen Chen, M.D., Devi SenGupta, M.D., Robert H. Hyland, D.Phil., Anu O. Osinusi, M.D., Huyen Cao, M.D., Christiana Blair, M.S., Xuelian Wei, Ph.D., Anuj Gaggar, M.D., Ph.D., Diana M. Brainard, M.D., William J. Towner, M.D., Jose Muñoz, M.D., Kathleen M. Mullane, D.O., Pharm.D., Francisco M. Marty, M.D., Karen T. Tashima, M.D., George Diaz, M.D., and Aruna Subramanian, M.D., for the GS-US-540-5773 Investigators*

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 1. Demographic and Clinical Characteristics of the Patients at Baseline According to Remdesivir Treatment Group.*

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

* 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).

Table 2. Clinical Outcomes According to Remdesivir Treatment Group.

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7. Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)
Clinical improvement — no. of patients (%)			
Day 5	33 (16)	29 (15)	0.2% (−7.0 to 7.5)
Day 7	71 (36)	54 (27)	−5.0% (−14.0 to 4.0)
Day 11	116 (58)	97 (49)	−4.8% (−14.1 to 4.6)
Day 14	129 (64)	107 (54)	−6.5% (−15.7 to 2.8)
Time to recovery (median day of 50% cumulative incidence‡)	10	11	0.81 (0.64 to 1.04)
Recovery — no. of patients (%)			
Day 5	32 (16)	27 (14)	0.1% (−7.0 to 7.1)
Day 7	71 (36)	51 (26)	−6.0% (−14.8 to 2.7)
Day 11	115 (58)	97 (49)	−3.7% (−12.8 to 5.5)
Day 14	129 (64)	106 (54)	−6.3% (−15.4 to 2.8)
Time to modified recovery (median day of 50% cumulative incidence‡)	9	10	0.82 (0.64 to 1.04)
Modified recovery — no. of patients (%)			
Day 5	51 (26)	41 (21)	−2.3% (−10.5 to 5.9)
Day 7	84 (42)	69 (35)	−3.4% (−12.6 to 5.8)
Day 11	128 (64)	106 (54)	−5.7% (−14.6 to 3.2)
Day 14	140 (70)	116 (59)	−6.7% (−15.3 to 1.9)

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.

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Results: Length of stay, mortality

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

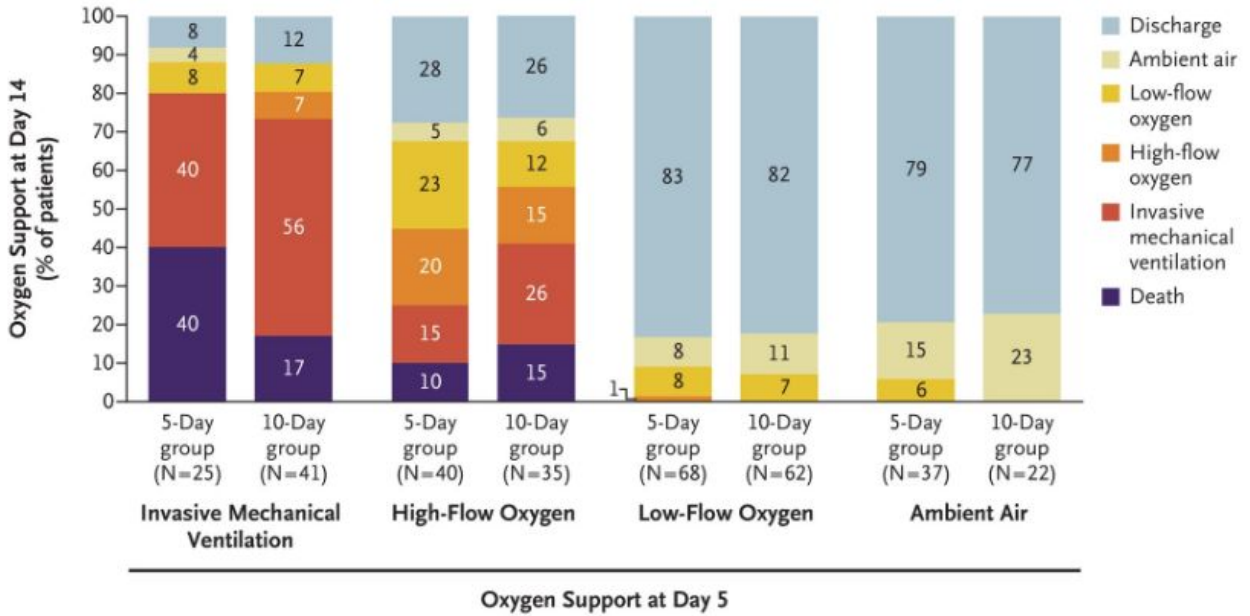
More patients were discharged from the hospital in the 5-day group than in the 10-day group

Mortality was numerically lower in 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%).

Measures	5 day tx	10 day tx
Duration of hospitalization	7 days	8 days
Percent discharged	60%	52%
Mortality	8%	11%

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

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%

Table 3. Summary of Adverse Events According to Remdesivir Treatment Group.*

Event or Abnormality	5-Day Group (N=200)	10-Day Group (N=197)
Any adverse event — no. of patients (%)	141 (70)	145 (74)
Nausea	20 (10)	17 (9)
Acute respiratory failure	12 (6)	21 (11)
Alanine aminotransferase increased	11 (6)	15 (8)
Constipation	13 (6)	13 (7)
Aspartate aminotransferase increased	10 (5)	13 (7)
Hypokalemia	10 (5)	12 (6)
Hypotension	9 (4)	12 (6)
Respiratory failure	7 (4)	14 (7)
Insomnia	10 (5)	11 (6)
Acute kidney injury	4 (2)	15 (8)
Adverse event leading to discontinuation of treatment — no. of patients (%)	9 (4)	20 (10)
Any serious adverse event	42 (21)	68 (35)
Acute respiratory failure	10 (5)	18 (9)
Respiratory failure	5 (2)	10 (5)
Septic shock	2 (1)	5 (3)
Acute respiratory distress syndrome	1 (<1)	5 (3)
Hypoxia	2 (1)	4 (2)
Respiratory distress	3 (2)	4 (2)
Dyspnea	4 (2)	1 (1)
Pneumothorax	2 (1)	3 (2)
Viral pneumonia	3 (2)	2 (1)
Aminotransferase levels increased	3 (2)	2 (1)

p=0.01

p=0.003

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

Any grade ≥3 laboratory abnormality — no. of patients/total no. (%)	53/195 (27)	64/191 (34)
Selected grade ≥3 laboratory abnormalities — no. of patients/total no. (%)		
Creatinine clearance decreased		
Grade 3	13/193 (7)	13/188 (7)
Grade 4	5/193 (3)	23/198 (12)
ALT elevation		
Grade 3	8/194 (4)	11/191 (6)
Grade 4	4/194 (2)	5/191 (3)
AST elevation		
Grade 3	11/194 (6)	7/190 (4)
Grade 4	3/194 (2)	4/190 (2)
Bilirubin increased		
Grade 3	1/193 (1)	3/190 (2)
Grade 4	0	1/190 (1)

p < 0.001

* Adverse events listed are those that occurred in at least 5% of patients in either treatment group, and serious adverse events listed are those that occurred in 5 or more patients.

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!

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