Keeping Up with COVID-19 Part 2: Revisiting Remdesivir

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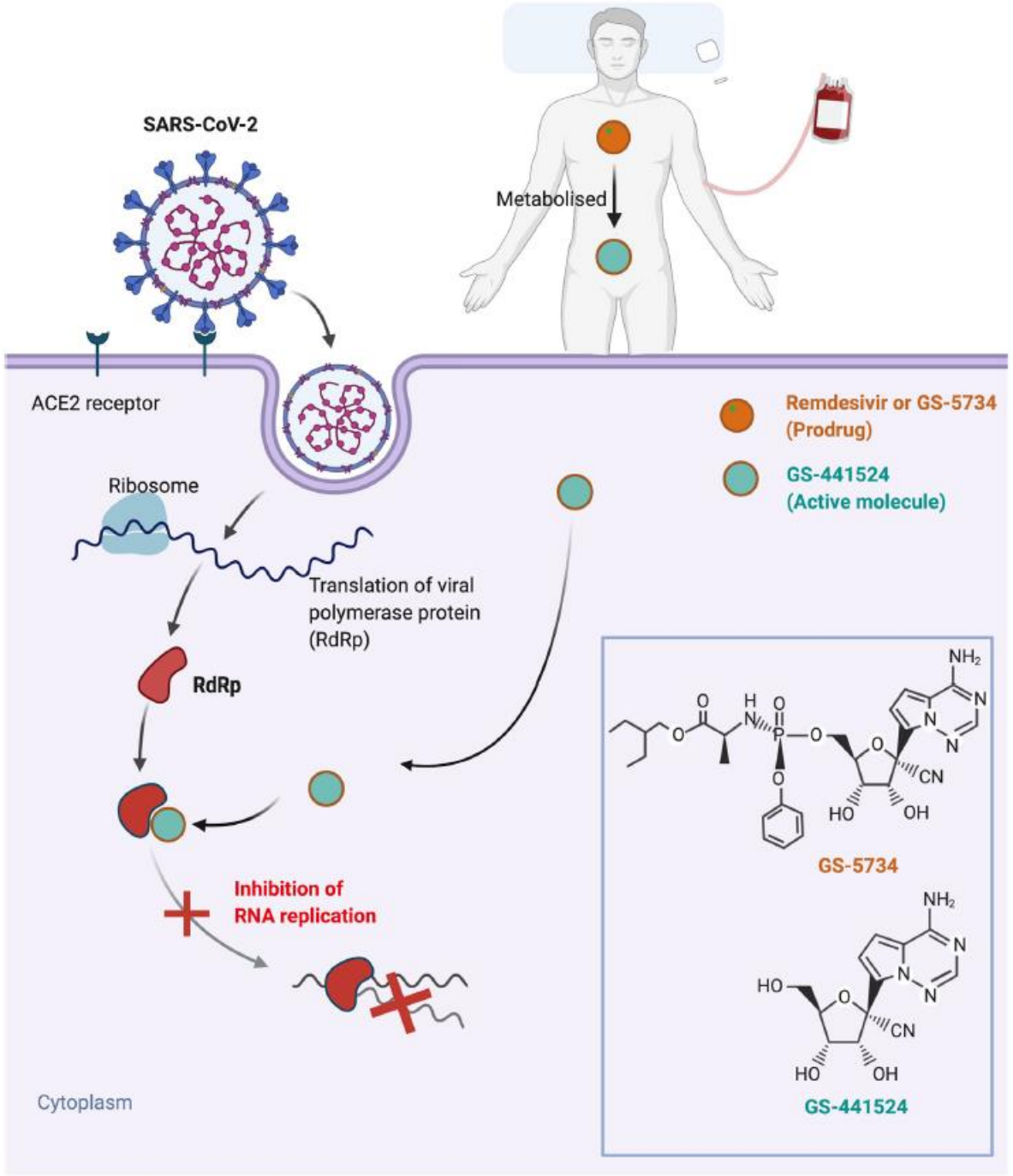
Last Updated 6/30/21

Remdesivir Mechanism of Action



https://doi.org/10.1016/j.cegh.2020.07.011

Remdesivir History

2014-2016	• Developed in response to Ebola outbreak in West Africa
5/1/2020	• Emergency Use Authorization (EUA) approved for use in hospitalized patients with severe COVID-19 disease
8/28/2020	• EUA revised to expand use for hospitalized COVID patients (no longer limited to severe disease)
10/22/2020	• FDA approval granted for use in adult and pediatric patients hospitalized with COVID-19

Summary of Key Remdesivir Trials

Trials	Evidence Summary
1. ACTT NEJM 2020	1. ACTT-1 (N =1062) → Remdesivir vs Placebo • Remdesivir significantly reduced time to recovery → Median 10 days vs. 15 days; recovery rate ratio 1.29; 95% CI, 1.12–1.49; P < 0.001 • Greatest benefit in patients requiring supplemental O2 → Survival benefit in post hoc analysis; HR for death 0.28; 95% CI, 0.12–0.66
2. Wang Y et al. Lancet 2020	2. Adults with Severe COVID (N= 237) → Remdesivir vs Placebo • Study terminated early (unable to meet target enrollment) • Trend towards faster time to clinical improvement when remdesivir started within 10 days of symptom onset → median of 18 days vs. 23 days; HR 1.52; 95% CI, 0.95–2.43
3. Spinner CD et al. JAMA 2020	3. Moderate COVID (N = 596) → Remdesivir 5 days or 10 days vs Standard of care (SOC) • 5 days of remdesivir demonstrated significant improvement in clinical status on day 11 vs SOC → OR 1.65; 95% CI, 1.09–2.48; P = 0.02 • No difference in clinical status with 10 days of remdesivir vs SOC → p= 0.18
4. Goldman JD et al. NEJM 2020	4. Remdesivir 5 days or 10 days (N = 402) • At baseline, participants in the 10-day group had worse clinical status than those in the 5-day group (P = 0.02) • Time to clinical improvement was similar (10 days vs 11 days)

1. https://www.ncbi.nlm.nih.gov/pubmed/32445440
2. https://www.ncbi.nlm.nih.gov/pubmed/32423584
3. https://www.ncbi.nlm.nih.gov/pubmed/32821939
4. https://www.ncbi.nlm.nih.gov/pubmed/32459919

Guideline Recommendations for Hospitalized Patients with COVID-19

Disease Severity	Infectious Diseases Society of America (IDSA)	National Institution of Health (NIH)
Mild to Moderate	Suggest against use in patients without a need for supplemental oxygen and SpO2 > 94%	Insufficient data to recommend for or against routine use. May be appropriate for patients at high risk of disease progression
Severe	Suggest use in patients with SpO2 $\leq$ 94% on room air	Recommend in patients that require supplemental oxygen
Critical	Suggests against routine initiation in patients in the ICU on invasive mechanical ventilation and/or ECMO, or in septic shock	Recommend against use as monotherapy and routine initiation in patients requiring mechanical ventilation or ECMO. May consider initiating in combination with dexamethasone for patients who have recently been intubated

NIH COVID-19 Treatment Guidelines: Accessed 6/30/2021
IDSA Treatment Guidelines for COVID-19: Accessed 6/30/2021

Real World Evaluation of Remdesivir Use: UF Health Central Florida

Multicenter (N = 2), retrospective observational study

Evaluated patients that received Remdesivir from 7/1/2020 to 2/28/2021

Enrolled a total of 100 patients (50 per campus)

Inclusion/ exclusion per EUA criteria

- 7/1/20 to 8/27/20 EUA criteria for severe COVID only
- 8/28/20 EUA revised to include all hospitalized patients

Groups were stratified based off of SpO2 and supplemental O2 requirement

- Group 1 < 94% SpO2 +/- supplemental O2 (N = 48)
- Group 2 > 94% SpO2 + supplemental O2 (N = 52)

Information curtsey of UF Health Central Florida

MUE: Baseline Demographics

Groups	Male	Female	Age > 65	PMH HTN	PMH HLD	PMH COPD	PMH DM
1 (48)	68.8%	39.6%	79.1%	70.8%	58.3%	25.0%	27.1%
2 (52)	70.8%	29.2%	84.6%	68.8%	52.1%	22.9%	20.8%

Groups	Age (Yrs)	Symptom Onset (Days)	C-Reactive Protein*# (N)	Procalcitonin # (N)
1 (48)	73.6	4.6	12.2 (45)	0.52 (41)
2 (52)	73.1	3.4	8.9 (51)	0.36 (45)

Average was taken for each category
* Was significant P < 0.05 (T-Test)
# Not every patient had a level drawn

Scale on Admission	Group 1 % (48)	Group 2 % (52)
2	0	3.8 (2)
3	37.5 (18)	36.5 (19)
4	62.5 (30)	57.7 (30)
5	0	1.9 (1)

Scale	Description
1	Poor prognosis, Expired
2	ICU requiring mechanical ventilation
3	ICU requiring supplemental oxygen
4	Non-ICU requiring supplemental oxygen
5	Non-ICU, not requiring supplemental oxygen, symptomatic, limited activities
6	Non-ICU, not requiring supplemental oxygen, symptomatic, some limitation to activities
7	Non-ICU not requiring supplemental oxygen, not symptomatic, no limitation to activities, discharged

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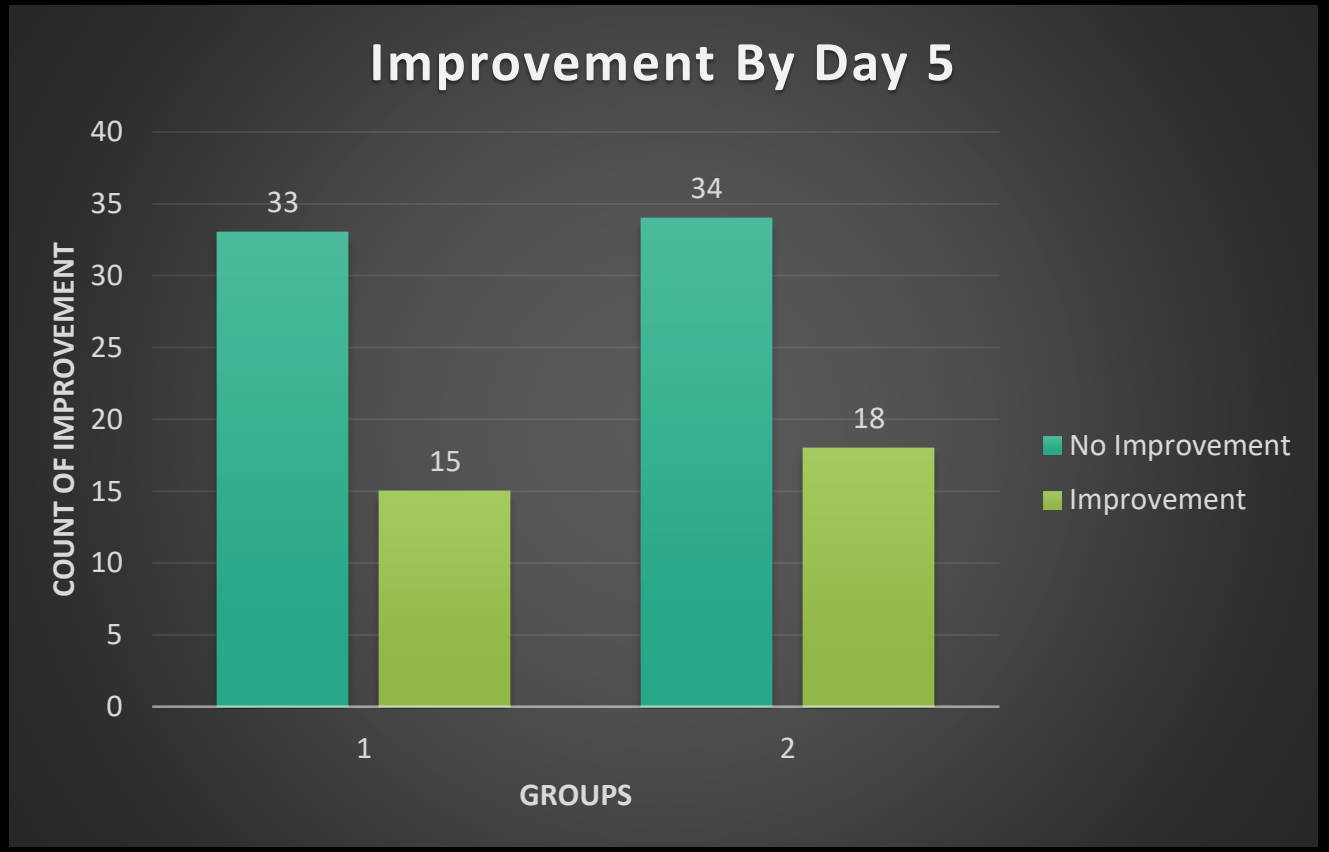
MUE Main Findings

Groups	Expired	DISCHARGE (STABLE)	LOS^ (N)
1 (48)	54.2%	45.8%	12.2 (22)
2 (52)	32.7%	67.3%	8.5 (35)

Chi Square Test used
^ Expired patients were excluded



P > 0.05
Not Significant

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Remdesivir Use in Patients with eGFR < 30 mL/min

- Remdesivir is not recommended in patients with eGFR < 30 mL/min per package insert
- Although < 10% of drug is renally excreted, 49% of active metabolites were recovered in urine in early pharmacokinetic (PK) studies
- IV formulation contains sulfobutylether-beta-cyclodextrin sodium (SBECD) which may accumulate in the setting of renal impairment
- Safety data has not been rigorously assessed in this population at this time
- Observational data suggests a lack of clinically significant adverse outcomes with sort term use (5-10 days)
- Gilead is currently enrolling for a PK study to help address this concern

Remdesivir Package insert: Accessed 6/30/2021
Jorgenson SCJ et al. Pharmacotherapy 2020; 40(7):659-671
Thakare S et al. Kidney Int Rep 2021 6;206-210

Remdesivir Summary

FDA approved for Treatment of COVID-19 Infection

- Hospitalized COVID positive patients
- Consider in patient with SpO2 $\leq$ 94% on room air or require an increase in supplemental oxygen from baseline

Exclusions for Use

- eGFR < 30 mL/min
- ALT/AST > 5 times upper limit of normal
- Allergy to remdesivir

Administration

- 200 mg IV on day 1 (loading dose), followed by 100 mg IV daily

Duration of Therapy

- 5 days or until hospital discharge, which ever comes first
- May consider extending up to a maximum of 10 days if patient does not clinically improve by day 5 or requires mechanical ventilation or ECMO

Additional monitoring

- Liver function (LFTs), renal function (SCr, BUN, eGFR), prothrombin time

Remdesivir Package insert: Accessed 06/27/2021

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