REMDESIVIR IN HOSPITALIZED COVID-19 PATIENTS: INDIVIDUAL PATIENT DATA META-ANALYSIS

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BACKGROUND

- The interpretation of the evidence from randomized clinical trials (RCTs) on remdesivir for hospitalized patients with coronavirus disease 2019 (COVID-19) is conflicting.
- We conducted a systematic review and **individual patient data meta-analysis (IPDMA) of RCTs** to assess the benefits and harms of **remdesivir** compared to placebo or usual care in **hospitalized patients** and whether treatment effects differed between **prespecified subgroups.**

METHODS

- We systematically searched PubMed, Embase, trial registries and preprint servers through April 11, 2022, and contacted authors of eligible trials to share individual patient data.
- The primary outcome was **all-cause mortality at day 28.**
- We used multivariable hierarchical regression and multivariable fractional polynomial interaction – adjusting for respiratory support, age, and enrollment period – to investigate effect modifiers and judged them using ICEMAN (*Schandelmaier S. et al. CMAJ 2020*)
- Protocol: PROSPERO (CRD42021257134)

Survival **benefit with remdesivir in patients with no or conventional oxygen support** and inconclusive evidence in patients with more intensified respiratory support. Remdesivir did **not increase** severe or serious **adverse events**.

RESULTS and CONCLUSIONS

- 9 eligible RCTs, 8 provided individual patient data for **10480 hospitalized COVID-19 patients** (**99% of total randomized patients globally**; Figure 1) between February 2020 and April 2021.
- Within 28 days of randomization, 662 of 5317 patients (12.5%) assigned to remdesivir and 706 of 5005 (14.1%) assigned to no remdesivir died (adjusted odds ratio **[aOR] 0.88;** 95% confidence interval [CI], **0.78-1.00**; p=0.045).
- Remdesivir did **not increase the frequency of severe or serious adverse events.**
- Strong evidence for a **credible subgroup effect according to respiratory support** at baseline (*p*-int 0.019, consistency across trials). No credible subgroup effect for age, comorbidities, corticosteroid use, C-reactive protein or humoral immune status.
- Some evidence for larger treatment effects if earlier remdesivir initiation after symptom onset, but insufficient consistency across trials and *p*-int 0.297 (assessed as linear trend) not credible enough.
- We summarized the effects stratified by respiratory support. Patients with no or conventional oxygen benefit from remdesivir (Table 1), for patients with more respiratory support evidence is inconclusive.

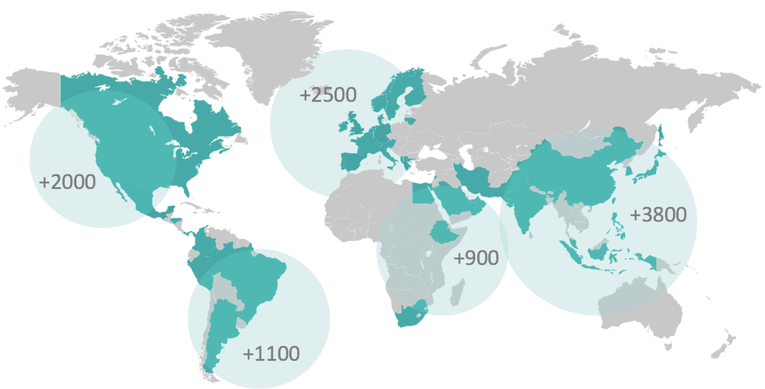

Figure 1: RCTs that provided individual patient data: ACTT-1 (n=1062), Wang et al (n=236), CATCO (n=1282), DisCoVeRy (n=843), FIN-Solidarity (n=208), NOR-Solidarity (n=99), Spinner et al (n=584), remaining WHO-Solidarity data (n=6167)

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Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty in Effect Estimates (Quality of Evidence)	Summary
		Remdesivir	No Remdesivir		
All-cause mortality at day 28	**aOR 0.80 (0.70-0.93)** Based on data from 8632 patients from 8 trials	92 per 1000	112 per 1000	High	Remdesivir reduces 28-day mortality in this patient subgroup
		Absolute Difference: 20 fewer per 1000 (95% CI, 31 fewer to 7 fewer); NNT 50 / If ACR 2.5%: NNT 205			
New mechanical ventilation or death at day 28	**aOR 0.78 (0.69-0.87)** Based on data from 8662 patients from 8 trials	155 per 1000	190 per 1000	High	Remdesivir reduces progression to mechanical ventilation or death
		Absolute Difference: 35 fewer per 1000 (95% CI, 51 fewer to 21 fewer)			
Days until discharge/ reaching discharge criteria up to day 28	**aHR 1.02 (0.98-1.07)** Based on data from 8737 patients from 8 trials	7 (median)	7 (median)	Moderate	Remdesivir probably has little or no effect on days until hospital discharge
		Absolute Difference: 0 day less (95% CI, 0 to 1 day more)			
Adverse event grade 3 or 4 or serious adverse event within 28 days	**aOR 0.82 (0.68-0.99)** Based on data from 2810 patients from 6 trials	214 per 1000	249 per 1000	Moderate	Remdesivir probably reduces the risk of severe and serious adverse events
		Absolute Difference: 35 fewer per 1000 (95% CI, 65 fewer to 2 fewer)			

Table 1: Summary of findings, following GRADE, for patients receiving no or only conventional oxygen support

NOTES:

Faster data sharing (> 1 year negotiation despite unambiguous data sharing statements in results publications) would have enabled **greater clinical impact.**

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