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Jean-Jacques Parienti, Harm-Jan de Grooth

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Jean-Jacques PARIENTI*[1,2], Harm-Jan DE GROOTH[3,4]

[1] Department of Infectious Diseases, University Hospital, Caen, France.

[2] INSERM U1311 DYNAMICURE, Université Caen Normandie, Caen, France.

[3] Amsterdam Infection and Immunity Institute, Amsterdam UMC, location VUmc, Amsterdam, the Netherlands.

[4] Department of Intensive Care, Amsterdam UMC, location VUmc, Vrije Universiteit Amsterdam, Amsterdam Cardiovascular Sciences, De Boelelaan 1117, Amsterdam, the Netherlands.

*Corresponding author: parienti-jj@chu-caen.fr

Phone: +33 231 06 43 20

Fax: +33 231 06 50 68

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Early reduction of SARS-CoV-2 viral replication emerges as a new strategy to reduce COVID-related morbidity and mortality[1]. Noteworthy, early observations[2] and models[3] have revealed an association between high SARS-CoV-2 nasopharyngeal RNA levels and high risk of hospitalization or death. How much this relationship relies on confounding is unknown. For example, age influences both viral clearance and the risk of adverse outcomes[3]. In clinical trials, testing the potential antiviral effect using SARS-CoV-2 RNA reduction endpoint appears as a logical first-step, but pivotal trials must demonstrate an effect on a clinically meaningful aspect of the disease[4]—that is, a patient-oriented endpoint[5]. To date, there is no established predictive relationship between the magnitude and timing of viral load reductions and the extent of clinical benefit. Nevertheless, Mitjà and collaborators[6] recommended 7 days as the optimal time for measurement and 0.5 $\log_{10}$ decrease or greater as the minimal threshold for significant reduction between arms.

As the number of trials in outpatients with COVID-19 grows, our understanding of the interplay between several endpoints will become clearer. We aimed to assess whether the effect of an antiviral therapy on the risk of hospitalization or death is predicted by the effect of a therapy on the nasopharyngeal SARS CoV-2 viral load.

We searched for phase 2/3 randomized controlled trials of drug therapies conducted amongst outpatients with COVID-19 reporting both: (i) the risk of hospitalization or death and (ii) the nasopharyngeal SARS-CoV-2 viral load change from baseline to day 5-7 (see details in the Supplemental appendix). The trial-level variability on the log-transformed relative risk of hospitalization or death explained by the treatment effects on the nasopharyngeal SARS CoV-2 viral load was quantified by R^2 through a random-effect linear regression model, weighted by trial size. We also established a Surrogate Threshold Effect (STE): the minimum treatment effect on nasopharyngeal viral load reduction (the surrogate outcome) necessary to predict a significant effect on hospitalization or death (the patient-oriented outcome). The STE was determined by the intersection of the upper 95% prediction limit and the horizontal line with a relative risk (RR) equal to one. Because pivotal trials stopped prematurely for benefit are associated with an overestimation of the effect size[7], we conducted a sensitivity analysis after excluding these trials, as recommended[8].

Sixteen studies testing 17 interventions in 14,010 COVID-19 outpatients reported both treatment effects on SARS-Cov-2 viral load and on relative risk of hospitalization or death. The baseline characteristics and extracted results from the included studies are shown in the Table S1 and Table S2. The relative risk of hospitalization or death amongst outpatients with COVID-19 was significantly (P=0.021) predicted by the magnitude of nasopharyngeal SARS-CoV-2 viral load reduction (Figure 1), corresponding to a moderate R^2 of 0.53. The STE corresponding to a non-zero effect on hospitalization or death was 0.41 $\log_{10}$ higher nasopharyngeal SARS-CoV-2 viral load reduction relative to placebo at day 5-7. Without PINETREE, the relative risk of hospitalization or death amongst outpatients with COVID-19 was more strongly (P=0.003) predicted by the magnitude of SARS-CoV-2 viral load reduction (Figure S1), corresponding to a good R^2 of 0.68. The STE remained similar (0.38 $\log_{10}$ reduction).

Reducing the SARS-CoV-2 viral load early is relevant and beneficial for outpatients with COVID-19. We acknowledge the measurement errors related to the quality of sampling specimen swab and the lack of a standardized quantitative PCR for nasopharyngeal SARS-CoV-2 RNA. However, these technical aspects can be controlled in the clinical research setting. Although the number of trials is small, this finding suggests that nasopharyngeal SARS-CoV-2 viral load reduction at days 5-7 captures at least half of the subsequent disease progression in outpatient COVID-19 trials. In addition, this result complements the FDA recommendation to select virologic outcome as a potential surrogate endpoints in phase 2 trials[9] to identify promising antiviral therapies against COVID-19[4] by providing data and a threshold above which clinical benefit is expected in phase 3 trials.

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Figure 1: Clinical benefit (Y-axis) by relative SARS-CoV-2 viral load reduction (X-axis) in outpatient COVID-19 trials. Point size is proportional to sample size. The vertical red dashed line denotes the surrogate threshold effect (STE): the minimum increase in viral load reduction necessary to predict a significant reduction in hospitalization or death.