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Research Letter | Critical Care Medicine

Efficacy of Acyclovir to Suppress Herpes Simplex Virus Oropharyngeal Reactivation in Patients Who Are Mechanically Ventilated

An Ancillary Study of the Preemptive Treatment for Herpesviridae (PTH) Trial

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Introduction

In the recently published Preemptive Treatment for Herpesviridae (PTH) randomized clinical trial (NCT02152358),¹ preemptive use of acyclovir for patients who were mechanically ventilated with oropharyngeal herpes simplex virus (HSV) reactivation failed to demonstrate a positive impact on day-60 ventilator-free days; however, a trend toward a decreased day-60 mortality rate was found in favor of acyclovir. However, the impact of acyclovir on oropharyngeal HSV reactivation was not assessed. We performed this retrospective study to evaluate the efficacy of acyclovir to suppress HSV oropharyngeal reactivation within the PTH trial.

Methods

This analysis of a randomized clinical trial was planned in the original protocol (available with the original publication and in [Supplement 1](#)),¹ which was approved by an independent ethics committee (Comité de Protection des Personnes Sud Méditerranée 5). Written informed consent was obtained from patients or their legally authorized representatives. For the latter, the patient's follow-up informed consent was obtained when possible. Conduct of the study and reports of results follow the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

The PTH trial was performed in 16 French intensive care units among 238 adults aged older than 18 years. Participants were mechanically ventilated for at least 96 hours, were expected to remain on mechanical ventilation for 48 hours or more, and had HSV oropharyngeal reactivation. Patients were randomized to receive acyclovir 5 mg/kg or a matching placebo 3 times daily for 14 days.¹

HSV shedding was assessed on prospectively collected oropharyngeal swabs from patients included in 2 centers (Hôpital Pitié-Salpêtrière, Paris, and Hôpital Nord, Marseille) at randomization and at days 7, 14, and 21 postrandomization. All patients with at least 1 follow-up swab were included in this study (eFigure in [Supplement 2](#)). Details regarding patient sampling and sample processing are available in eMethods in [Supplement 2](#).

Data are expressed as median (IQR), mean (SD), or mean with 95% CI, as appropriate. Between-group comparisons used Student *t* test or Mann-Whitney *U* test for continuous variables according to variable distribution (ie, normal or not normal). For categorical variables, between-group comparisons used χ^2 or Fischer exact tests. All analyses were computed with R software version 3.5.1 (R Project for Statistical Computing) at a 2-sided 5% level of significance. Data were analyzed from February through April 2021. Further details regarding statistical analysis are given in eMethods in [Supplement 2](#).

Results

Among 239 patients included in the PTH trial, 133 patients were included in the 2 centers participating in this ancillary study; among these patients, 130 individuals (87 patients in Paris and 43

+ Supplemental content

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patients in Marseille) had at least 1 follow-up swab and were included in the study. Patient baseline characteristics were comparable between groups; among 66 patients in the acyclovir group and 64 patients in the placebo group, there were 43 (65.2%) men and 46 (71.9%) men, respectively. The groups had a median (IQR) age of 59 (50-66) years and 59 (43-66) years, admission simplified acute physiology score II of 42 (35-54) and 43 (36-50), and admission sequential organ failure assessment score of 10 (7-13) and 9 (7-12), respectively. Median (IQR) body mass index (calculated as weight in

Table. Cumulative Incidence of HSV Shedding, Extubation, and Death

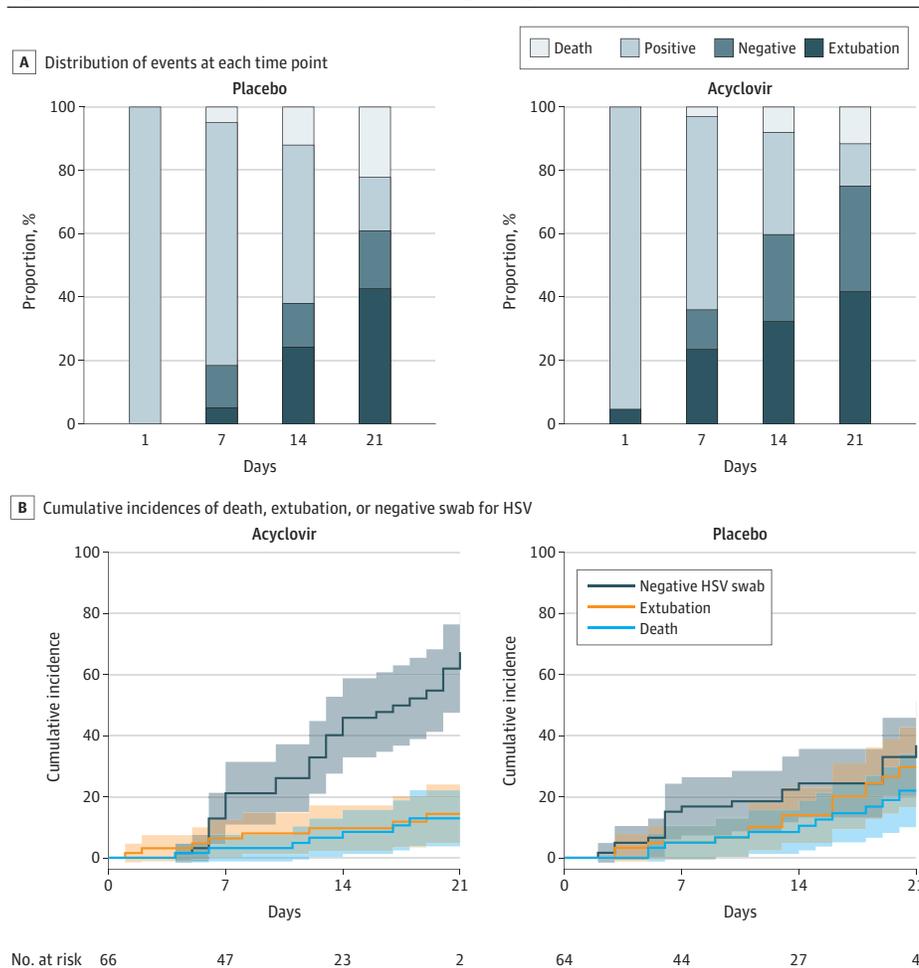
Outcome and treatment group	Cumulative incidence, % (95% CI)				P value
	Day 1 ^a	Day 7	Day 14	Day 21	
HSV-negative swab					
Acyclovir	0	0.21 (0.12-0.32)	0.46 (0.33-0.58)	0.67 (0.49-0.81)	.008
Placebo	0	0.17 (0.09-0.27)	0.24 (0.14-0.36)	0.37 (0.23-0.51)	
Extubation					
Acyclovir	0.02 (0.00-0.08) ^b	0.06 (0.02-0.14)	0.10 (0.04-0.13)	0.14 (0.07-0.25)	.11
Placebo	0	0.05 (0.01-0.13)	0.14 (0.06-0.24)	0.29 (0.17-0.43)	
Death					
Acyclovir	0	0.03 (0.01-0.10)	0.09 (0.03-0.17)	0.13 (0.06-0.24)	.29
Placebo	0	0.05 (0.01-0.13)	0.11 (0.04-0.02)	0.22 (0.11-0.35)	

Abbreviation: HSV, herpes simplex virus.

^a Day 1 is the day of randomization.

^b One patient was extubated on the day of randomization.

Figure. Kinetics of Herpes Simplex Virus (HSV) Shedding During First 21 Days After Randomization



kilograms divided by height in meters squared) differed significantly between groups: 29.5 (26.2-34.4) for the acyclovir group vs 26.8 (23.4-31.4) for the placebo group.

Proportions of patients who were deceased or extubated were not significantly different from day 1 to day 21 in the acyclovir or placebo groups. However, the cumulative incidence of patients with HSV-negative oropharyngeal swabs was significantly increased in the acyclovir group from randomization to day 21 compared with the placebo group (from 0% at randomization to 67.3% at day 21 [95% CI, 49.0%-81.0%] in the acyclovir group vs 0% at randomization to 36.8% [95% CI, 23.0%-51.0%] at day 21 in the placebo group; $P = .008$) (Table and Figure). Subdistribution hazard ratios for acyclovir vs placebo obtained from the Fine-Gray model for HSV negative swab, extubation, and death were 2.50 (95% CI, 1.42-4.39), 0.41 (95% CI, 0.17-0.96), and 0.52 (95% CI, 0.20-1.35), respectively.

Discussion

This analysis of a randomized clinical trial found that intravenous acyclovir at a dosing of 15 mg/kg/d for 14 days was effective in decreasing the duration of HSV oropharyngeal shedding compared with placebo among patients mechanically ventilated for 96 hours or more. However, throat HSV shedding was still detected among one-third of patients after 14 days of antiviral treatment. In the parent trial,¹ patients in the acyclovir group had a decreased mortality rate but increased duration of mechanical ventilation.

One hypothesis for the negative result of the PTH trial was the inefficacy of acyclovir to cure HSV oropharyngeal reactivation,¹ although this drug has been shown to prevent HSV reactivation.² Although we found here that acyclovir allowed the shortening of HSV shedding duration, this dosing and duration of antiviral treatment do not appear to be sufficient to totally suppress oropharyngeal HSV reactivation and shedding among patients who are mechanically ventilated. Whether increased doses and prolonged duration of treatment may lead to complete suppression of HSV shedding and may improve outcomes remains to be determined. Limitations of our study include the limited number of patients included and missing samples.

ARTICLE INFORMATION

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Author Contributions: Dr Luyt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Luyt.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Luyt.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Hajage, Diallo.

Obtained funding: Papazian.

Administrative, technical, or material support: Luyt, Burrel, Papazian, David.

Supervision: Luyt, Hajage, Hraiech.

Conflict of Interest Disclosures: Dr Luyt reported receiving personal fees from Bayer Healthcare, Merck, Thermo Fisher Brahms, Carmat, Biomérieux, and Aerogen outside the submitted work. Drs Hajage and Papazian reported receiving grants from the French Ministry of Health during the conduct of the study. No other disclosures were reported.

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Trial Registration: ClinicalTrials.gov Identifier: [NCT02152358](https://clinicaltrials.gov/ct2/show/study/NCT02152358)

Data Sharing Statement: See [Supplement 3](#).

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SUPPLEMENT 1.

Trial Protocol

SUPPLEMENT 2.

eMethods.

eFigure. Study Flowchart

SUPPLEMENT 3.

Data Sharing Statement