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A Randomized Clinical Trial

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IMPORTANCE The role of herpes simplex virus (HSV) reactivation on morbidity and mortality in patients in the intensive care unit requiring mechanical ventilation remains unknown.

OBJECTIVE To determine whether preemptive treatment with intravenous acyclovir reduces the duration of mechanical ventilation in patients with HSV oropharyngeal reactivation.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, placebo-controlled randomized clinical trial was conducted in 16 intensive care units in France. Participants included 239 adults (age, >18 years) who received mechanical ventilation for at least 96 hours and continued to receive mechanical ventilation for 48 hours or more, with HSV oropharyngeal reactivation. Patients were enrolled between February 2, 2014, and February 22, 2018.

INTERVENTIONS Participants were randomized to receive intravenous acyclovir, 5 mg/kg, 3 times daily for 14 days or a matching placebo.

MAIN OUTCOMES AND MEASURES The primary end point was ventilator-free days from randomization to day 60. Prespecified secondary outcomes included mortality at 60 days. Main analyses were conducted on an intention-to-treat basis.

RESULTS Of 239 patients enrolled and randomized, 1 patient withdrew consent, leaving 238 patients, with 119 patients in both the acyclovir and placebo (control) groups (median [IQR] age, 61 [50-70] years; 76 [32%] women) available for primary outcome measurement. On day 60, the median (IQR) numbers of ventilator-free days were 35 (0-53) for acyclovir recipients and 36 (0-50]) for controls (P = .17 for between-group comparison). Among secondary outcomes, 26 patients (22%) and 39 patients (33%) had died at day 60 (risk difference, 0.11, 95% CI, -0.004 to 0.22, P = .06). The adverse event frequency was similar for both groups (28% in the acyclovir group and 23% in the placebo group, P = .40), particularly acute renal failure post randomization affecting 3 acyclovir recipients (3%) and 2 controls (2%). Four patients (3%) in the acyclovir group vs none in the placebo group stopped the study drug for treatment-related adverse events.

CONCLUSIONS AND RELEVANCE In patients receiving mechanical ventilation for 96 hours or more with HSV reactivation in the throat, use of acyclovir, 5 mg/kg, 3 times daily for 14 days, did not increase the number of ventilator-free days at day 60, compared with placebo. These findings do not appear to support routine preemptive use of acyclovir in this setting.

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Among the Herpesviridae responsible for infections in humans, herpes simplex virus (HSV) is one of the most frequent, with 50% to 80% of healthy adults being infected, most during childhood, and carrying the virus. Critical illness and mechanical ventilation, with endotracheal tube-induced microtrauma, are factors strongly associated with reactivation HSV in nonimmunocompromised patients. Oropharyngeal HSV reactivation occurs in 20% to 50% of mechanically ventilated patients, with the virus being detectable in up to 64% of patients receiving prolonged mechanical ventilation. Some patients develop true HSV bronchopneumonitis.[1,2] Moreover, HSV detection in the lower respiratory tract and HSV bronchopneumonitis seem to be associated with poorer outcomes in observational studies and a meta-analysis.[1-4] However, whether HSV reactivation in intensive care unit (ICU) patients occurs in the most severely ill patients, thus considered a marker of severity, or is associated with morbidity and mortality and treatment with acyclovir could improve the prognosis remain to be determined. We designed the Preemptive Treatment for Herpesviridae trial to determine whether treating mechanically ventilated HSV-reactivation-positive patients with acyclovir would improve their outcomes.

Key Points

Question Does preemptive treatment with acyclovir reduce the duration of mechanical ventilation in critically ill patients with herpes simplex virus oropharyngeal reactivation?

Findings In this multicenter, randomized clinical trial of 238 adults, treatment with intravenous acyclovir vs placebo during 14 days did not significantly reduce ventilator-free days at day 60. Compared with placebo, intravenous acyclovir was not associated with higher incidence of adverse events.

Meaning The findings of this study do not appear to support routine preemptive use of acyclovir in this setting.

Methods

Study Design

This randomized, multicenter, double-blind, placebo-controlled trial was conducted in 16 intensive care units (ICUs) in France from February 2, 2014, to February 22, 2018. An independent ethics committee (Comité de Protection des Personnes Sud Méditerranée 5) approved the study protocol, which is available with the statistical analysis plan - . Written informed consent was obtained from the patient or his or her legally authorized representative. For the latter, the patient's follow-up informed consent was obtained when possible. Participants did not receive financial compensation. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials.[5]

During the study period, potentially eligible patients (ie, those mechanically ventilated for ≥96 hours) were screened twice weekly with quantitative polymerase chain reaction performed on whole blood for cytomegalovirus (CMV) and qualitative polymerase chain reaction performed on oropharyngeal swabs for HSV reactivations. Patients with HSV-positive oropharyngeal swabs were potentially eligible for this trial. Patients could not be included in another study. Patients and/or their relatives were informed of this screening until December 18, 2015, when screening became routine care and French law rendered informing them no longer necessary.

Study Participants

Patients aged 18 years or older who had been receiving mechanical ventilation for 96 hours or more, with a predicted mechanical ventilation duration of 48 hours or more and an HSV-positive oropharyngeal swab, were eligible for enrollment. Exclusion criteria were use of acyclovir, ganciclovir, or another antiviral with anti-HSV activity (eg, cidofovir or foscavir) at the time of randomization; known hypersensitivity to acyclovir; active HSV or CMV infection treated during the preceding month; pregnancy or lactation; pancytopenia; solid-organ or bone-marrow transplant; immunosuppressant therapy (including corticosteroids at doses ≥0.5 mg/kg per day of prednisone or its equivalent for >1 month); HIV infection; moribund condition, defined as a preinclusion Simplified Acute Physiology Score (SAPS) II of 75 or higher (possible score, 0-163; where higher scores indicate greater disease severity)[6]; decision made to withhold or withdraw life-sustaining therapies; and ICU readmission during the same hospital stay.

Randomization

A centralized, secure, web-based randomization system using minimization assigned patients at a 1:1 ratio, with stratification by study site, prerandomization mechanical ventilation duration (≤14 or >14 days), and number of organ failures according to the Sequential Organ-Failure Assessment[7] (SOFA) score (<2 or ≥2). The SOFA score was calculated from 6 variables the day of randomization, taking into account the worst values of each parameter in the 24 hours preceding the randomization. Scores range from 0 to 24, with higher scores indicating more severe organ failure and higher mortality risk. Organ and system failure were deemed present when the corresponding SOFA score was greater than 2. All investigators, statisticians, and data analysts were blinded to arm assignments until the study and analysis were completed.

Study Interventions

Patients were randomized to receive intravenous acyclovir, 5 mg/kg, 3 times daily or a matching placebo preparation (controls) every 8 hours for a maximum duration of 14 days. That dose was chosen because it is recommended to treat immunocompromised patients' cutaneous HSV infections and has been shown to effectively prevent HSV reactivation in a previous randomized clinical trial.[8] For extubated patients discharged from the ICU before day 14 post randomization, the study agent was stopped at discharge. Acyclovir doses were adjusted to renal function according to the manufacturer's recommendations.[9] Placebo and acyclovir powders were conditioned in similar opaque bottles that were distributed post

randomization and reconstituted in saline by the nurses before each administration.

By November 16, 2016, although 206 patients had been randomized, the dates of validity of the initially manufactured opaque bottles that contained either the placebo or acyclovir powder had expired. Because funding for replacing the powders was not available, it was decided to continue the trial only in the 2 centers with the highest inclusion rates—Hôpitaux Universitaires Pitié Salpêtrière-Charles Foix and Hôpitaux de Marseille—and to use a different placebo and acyclovir distribution procedure that would keep investigators blind without requiring additional budget. Accordingly, from November 16, 2016, to the end of the trial, when a patient was randomized in the trial, acyclovir was reconstituted in saline bags by a pharmacist or an independent research nurse (both not blinded to the randomization arm) outside of the ICU. The same process was used for the placebo, and bags were distributed to the nurse in charge of the patient. All bags were labeled using protocol labels of Preemptive Treatment for Herpesviridae study drug. As such, the nurses and physicians in charge of the patients in the ICU were not aware of the study drug during the entire study period.

Study Outcomes

The primary outcome was the number of ventilator-free days at day 60 (ie, days alive without mechanical ventilation). For patients who died before day 60, that number was zero, regardless of mechanical ventilation duration. For patients with multiple mechanical ventilation episodes during the 60-day follow-up period, days without mechanical ventilation were considered only after the last weaning process of mechanical ventilation. Secondary outcomes included day 60 mortality rate; mechanical ventilation duration; occurrence of HSV bronchopneumonitis[2] or active CMV infection; secondary bacterial pneumonia, bacteremia, or fungemia; acute respiratory distress syndrome; and septic shock post randomization. The main safety end points were acute renal failure and neurotoxicity. The protocol specified that acyclovir could be stopped for stage 3 acute kidney injury as defined by the acute kidney injury network, if the treating physician judged it to be study agent related.[10] Potential neurologic complications were accorded special attention. Physicians recorded other safety concerns in the electronic case report form.

The following post hoc analyses were conducted: per-protocol analysis, including patients who had received the study agent for 7 days or more; subgroup analyses according to the number of organ failures at randomization (≤2 or >2) and number of prerandomization days on mechanical ventilation (defined according to the median value of 10 days); subgroup analyses according to the time of randomization (ie, before and after November 16, 2016, corresponding to the time of dispensation of study drug changed); and sensitivity analysis comparing the cumulative incidence of each event (mechanical ventilation weaning and death) to take into account the competition between these 2 events (ie, the occurrence of one type of event [eg, death] will prevent the occurrence of the other [mechanical ventilation weaning]).[11] Data on day 90 status and day 60 to 90 mechanical ventilation use were collected retrospectively to calculate day 90 mortality, day 90 ventilator-free days, and mechanical ventilation duration.

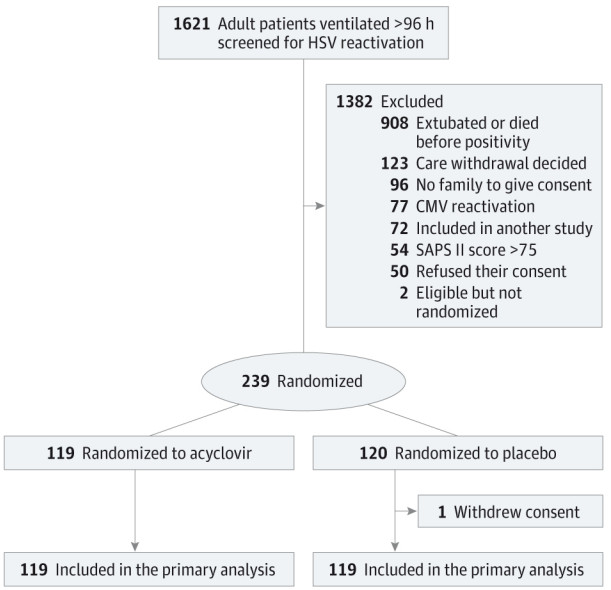
Statistical Analysis

According to a previous study evaluating HSV reactivation in patients with prolonged mechanical ventilation, the expected SD of ventilator-free days for controls was 20 days.[2] We hypothesized that preemptive acyclovir administration could increase the number of ventilator-free days by 8 days. To have 80% power with a 5% α level, 112 patients had to be included per group after applying a correcting coefficient of 0.864 to adjust for asymptotic test efficiency.[12] To account for potential losses to follow-up, that number was raised to 120 per group, meaning that 240 patients had to be included. Because 1 patient withdrew consent, the database was reset at 241 patients for stopping the inclusions. Two patients were inadvertently entered into the web randomization system but were not randomized because they fulfilled an exclusion criterion. When 241 patients were included in the web randomization system, the data manager stopped the inclusions, leaving 239 patients randomized and 2 not randomized.

As proposed recently, we recalculated ventilator-free days in such a manner that death constituted a worse outcome than fewer days off the ventilator.[13] Each patient was compared with every other patient in the study and assigned a score (tie: 0, win: +1, loss: −1) for each pairwise comparison based on who fared better. If one patient survived and the other did not, scores of +1 and −1 were assigned, respectively, for that pairwise comparison. If both patients in the pairwise comparison survived, the assigned score depended on which patient had more days free from mechanical ventilation: the patient with more days off the ventilator received a score of +1, and the patient with fewer days received a score of −1. If both patients survived and had the same number of days off the ventilator or if both patients died, they both were assigned a score of 0 for that pairwise comparison. For each patient, scores for all pairwise comparisons were summed, resulting in a cumulative score for each patient. These cumulative scores were ranked and compared between treatment groups via the Mann-Whitney technique. The probability of more favorable outcome is a ranked composite incorporating death and days free from mechanical ventilation among survivors. It represents the estimated probability that an individual randomly selected from 1 treatment group will have a higher score (more favorable outcome) than an individual randomly selected from the other group. It is mathematically equivalent to the area under the receiver operating characteristic curve for the Mann-Whitney test. A value of 50% indicates no difference between groups.[13]

Data are expressed as median (interquartile range [IQR]), mean (SD), or mean (95% CI), as appropriate. Between-group comparisons used a *t* test or the Mann-Whitney test for continuous variables according to the variable distribution (ie, normal or not). The normality assumption was tested for each quantitative variable using a Shapiro test if 1 of the numbers was less than 50 or an Anderson-Darling test. If normality was not rejected, we used the *t* test; otherwise, the Mann-Whitney test was used. For categorical variables, between-

Figure 1. Study Flowchart



The Simplified Acute Physiology Score (SAPS) II is assessed on a scale ranging from 0 to 163, with higher scores indicating greater disease severity.
CMV indicates cytomegalovirus; HSV, herpes simplex virus.

group comparisons used χ^2 or Fischer exact tests. Censored outcomes (time to death and time to weaning-off mechanical ventilation) were described with the Kaplan-Meier method, with between-group log-rank test comparisons. Proportional hazards assumption was evaluated graphically using Shoenfeld residuals and the Harrell test. Main analyses were conducted on an intention-to-treat basis.

All analyses were computed with R software, version 3.5.1 (R Project for Statistical Computing), at a 2-sided, 5% α level of significance.

Results

Among the 1621 patients screened for HSV and CMV, 239 were randomized (**Figure 1**). One placebo-group patient withdrew consent, leaving 238 assessable patients: 119 acyclovir and 119 placebo recipients. Participants' baseline characteristics at ICU admission (**Table 1**) differed significantly only for body mass index, which was lower for controls (median [IQR]: acyclovir, 29.3 [26.1-34.3] vs control: 27.2 [23.5-32.1]; calculated as weight in kilograms divided by height in meters squared). Their characteristics at randomization were also comparable (**Table 2**). The median (IQR) prerandomization mechanical ventilation duration was 10 (8-14) days for both groups.

Study Drug

All patients received 1 or more doses of a study agent. Median (IQR) treatment durations were comparable (**Table 3**): 14 (11-14) days for acyclovir recipients and 14 (10-14) days for controls (P = .69). Ninety patients (43 acyclovir recipients and 47 controls) stopped the study agent earlier than scheduled. Reasons for discontinuation were 25 deaths (acyclovir, 9; control, 16), 41 ICU discharges (acyclovir, 21; control, 20), 4 acyclovir-related adverse events, HSV bronchopneumonitis in a control patient, active CMV infection or herpes zoster in 2 control patients, 9 physicians' decisions (acyclovir, 4; control, 5), 4 errors (acyclovir, 3; control, 1), 3 unavailable study agents (acyclovir, 2; control, 1), and 1 unknown reason in a control patient.

Primary and Secondary End Points

On day 60, the median (IQR) numbers of ventilator-free days were 35 (0-53) for acyclovir recipients and 36 (0-50) for controls (P = .17 for between-group comparison).

On day 60, 26 acyclovir recipients (22%) and 39 controls (33%) had died (risk difference, 0.11; 95% CI, -0.004 to 0.22; P = .06). The hazard ratio for death within 60 days post randomization for the acyclovir group vs controls was 0.61 (95% CI, 0.37-0.99; P = .047) (**Figure 2**). No significant violation from the proportional hazards assumption was observed (P = .25). On day 60, 33 acyclovir recipients (28%) and 48 control patients (40%) had died or were still receiving mechanical ventilation (P = .08). Median (IQR) mechanical ventilation duration for day-60 survivors was 17 (6-32) days for acyclovir recipients and 14 (825) days for controls (P = .89). Other secondary end points (Table 3) did not differ between groups. Time to weaning from mechanical ventilation was comparable for the 2 groups (eFigure 1 .

Patients' clinical courses, as assessed by temperature, white blood cell count, radiologic score,[15] and modified Clinical Pulmonary Infection Score[16] from randomization to day 14, and SOFA score and Pao_2/fraction of inspired oxygen ratio kinetics from randomization to day 28 were also comparable for the 2 study groups (eFigures 2-7 . Microorganisms responsible for bacteremia/fungemia post randomization were also similar between groups (eTable 1

Post Hoc Analyses

The ranked composite end point, incorporating death and days free from mechanical ventilation through day 28, was not significantly different between treatment groups (Table 3). The probability of more favorable outcome with acyclovir compared with placebo was 51%. Subgroup analyses, reported in eTable 2, eTable 3, and eFigure 8 showed a significant interaction between day 60 mortality and number of organ failures at randomization but not mechanical ventilation duration before randomization, no significant interaction between ventilator-free days and the number of organ failures at randomization or mechanical ventilation duration before randomization, and no significant interaction between time of randomization and ventilator-free days or day 60 mortality. Sensitivity analysis comparing the cumulative incidence of mechanical ventilation weaning and death displayed similar results (eFigure 9 .

On day 90, 33 acyclovir recipients (28%) and 41 controls (34%) had died (P = .26 for between-group comparison) (eFigure 10 . The median (IQR) numbers of day 90 ventilator-free days were comparable for acyclovir recipients (32 [0-53]) and controls (36 [0-50]) (P = .43).

Table 1. Patient Characteristics at ICU Admission[a]

Characteristic	Study Group	
	Acyclovir (n = 119)	Placebo (n = 119)
Age, median (IQR), y	61 (52-68)	61 (48-71)
Men, No. (%)	78 (66)	84 (71)
Women, No. (%)	41 (34)	35 (29)
BMI, median (IQR)	29.3 (26.1-34.3)	27.2 (23.5-32.1)
McCabe and Jackson score >2, No. (%)[b]	30 (25)	26 (22)
Preexisting disease, No. (%)		
NYHA III or IV heart failure	5 (4)	8 (7)
Cancer/hemopathy	19 (16)	16 (13)
Diabetes	24 (20)	31 (26)
COPD	23 (19)	14 (12)
Cirrhosis	2 (2)	4 (3)
Chronic renal failure[c]	16 (13)	13 (11)
Admission category, No. (%)		
Medical	99 (83)	96 (81)
Emergency surgery	12 (10)	14 (12)
Planned surgery	8 (7)	9 (8)
Primary reason for mechanical ventilation, No. (%)		
Septic shock	16 (13)	17 (14)
Cardiogenic shock	12 (10)	14 (12)
Shock, other	1 (1)	2 (2)
Acute respiratory failure	31 (26)	25 (21)
Postoperative acute respiratory failure	6 (5)	12 (10)
Exacerbation of chronic respiratory disease	12 (10)	9 (8)
Trauma	5 (4)	5 (4)
Coma	6 (5)	9 (8)
Cardiac arrest	5 (4)	5 (4)
Other	25 (21)	21 (18)
SAPS II, median (IQR)[d]	45 (35-57)	46 (37-57)
SOFA score, median (IQR)[e]	10 (6-13)	9 (7-12)
Organ or system failure, No. (%)[f]		
Cardiovascular	72/117 (62)	77/117 (66)
Respiratory	82/112 (73)	80/113 (71)
Renal	47 (40)	43 (36)
Central nervous	23/117 (20)	27 (23)
Hepatic	1 (1)	4 (3)
Coagulation	6 (5	8 (7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ-Failure Assessment.

[a] There were no significant between-group differences in characteristics at ICU admission, except for body mass index (P = .002).

[b] Denotes the severity of underlying medical conditions: 0 indicates no underlying disease; 1, nonfatal underlying disease; 2, ultimately fatal (survival >1 to <5 years) underlying disease; and 3, rapidly fatal (survival <1 year) underlying disease.

[c] Creatinine clearance less than 60 mL/min, serum creatinine level greater than 1.7 mg/dL (to convert to micromoles per liter, multiply by 88.4), or chronic dialysis.

[d] Possible score, 0 to 163; higher scores indicate greater disease severity.

[e] Calculated from 6 variables the day of randomization, taking into account the worst values of each parameter in the 24 hours preceding the randomization. Scores range from 0 to 24, with higher scores indicating more severe organ failure and higher mortality risk. Patients with a SOFA score of 10 have a predicted mean chance of survival between 40% and 50%.

[f] Organ or system failure was deemed present when the corresponding SOFA score was greater than 2. When data regarding organ/system failure were missing, number of assessable patients is reported.

The per-protocol analysis that included patients treated for 7 days or more retained 227 patients: 111 acyclovir recipients and 116 controls. On day 60, the median numbers of ventilator-free days were 31 (0-50) for acyclovir recipients and 34 (0-50) for controls (P = .42). Among those 237 patients, 26 acyclovir recipients (23%) and 39 controls (34%) had died by day 60 (P = .09).

Table 2. Patient Characteristics at Randomization[a]

Characteristic	Study Group	
	Acyclovir (n = 119)	Placebo (n = 119)
MV duration before inclusion, median (IQR), d	10 (8-14)	10 (8-14)
Time between positive HSV test and randomization, median (IQR), d	3 (1-4)	2 (1-5)
Ongoing antimicrobial treatment, No. (%)	88 (74)	84 (71)
ECMO use, No. (%)	40 (34)	31 (26)
Renal replacement therapy, No. (%)	36 (30)	29 (24)
SOFA score, median (IQR)[b]	7 (5-10)	8 (5-11)
Organ or system failure, No. (%)[c]		
Cardiovascular	47 (40)	53 (45)
Respiratory	69 (58)	76 (64)
Renal	38 (32)	32 (27)
Central nervous	19 (16)	26 (22)
Hepatic	7 (6)	7 (6)
Coagulation	13 (11)	9 (8)
Temperature, median (IQR), °C	37.6 (36.6-38.2)	37.8 (37.1-38.5)
White blood cell count, median (IQR), /µL	12 900 (10 100-17 700)	13 900 (10 400-20 300)
Neutrophil count, median (IQR), /µL	9900 (7500-14 200)	11 500 (8700-16 900)
Pao_2/FiO_2, median (IQR), mm Hg	178 (87-246)	174 (114-230)
Radiologic score, median (IQR)	5 (2-8)	6 (3-8)

Abbreviations: ECMO, extracorporeal membrane oxygenation; HSV, herpes simplex virus; IQR, interquartile range; MV, mechanical ventilation; Pao_2/FiO_2 (fraction of inspired oxygen), partial oxygen pressure in arterial blood/fraction of inspired oxygen ratio; SOFA, Sequential Organ-Failure Assessment.

SI conversion: To convert neutrophils and white blood cells to $\times 10^9$ per liter, multiply by 0.001.

[a] There were no significant between-group differences in characteristics at randomization.

[b] Calculated from 6 variables the day of randomization, taking into account the worst values of each parameter in the 24 hours preceding the randomization. Scores range from 0 to 24, with higher scores indicating more severe organ failure and higher mortality risk. Patients with a SOFA score of 7 to 8 have a predicted mean chance of survival between 15% and 20%.

[c] Organ or system failure was deemed present when the corresponding SOFA score was greater than 2.

Safety

The adverse event rates were comparable for the 2 groups (eTable 4 , notably with 3 acyclovir recipients (3%) and 2 controls (2%) experiencing acute renal failure after randomization. Moreover, creatinine levels from randomization to day 14 for the 2 groups did not differ significantly (eFigure 11) and the percentages of patients requiring renal replacement therapy from randomization to end of treatment were comparable (eTable 5). No neurologic adverse event was reported by the investigators during the study, and Glasgow Coma Scale score changes from day 1 to day 14 were comparable for the groups (eFigure 12 i). Total bilirubin levels and platelet counts from day 1 to day 28 did not differ between groups (eFigure 13 and eFigure 14 , respectively). Four patients (3%) in the acyclovir group vs none in the placebo group stopped the study drug for treatment-related adverse events.

Discussion

Our study results show that preemptive acyclovir administration, compared with placebo for mechanically ventilated patients with oropharyngeal HSV reactivation, was not associated with shorter mechanical ventilation durations, as assessed by the number of ventilator-free days. Moreover, other secondary outcomes did not differ between acyclovir recipients and controls. Nonsignificant lower day 60 mortality was observed for acyclovir recipients compared with controls. Acyclovir was well tolerated at the dose administered (5 mg/kg 3 times daily), without renal or neurologic adverse events, although our study was underpowered to assess such major complications.

Reactivation of HSV is frequent in ICU patients and associated with increased morbidity[2] and mortality.[4] However, the exact effect of HSV reactivation in ICU patients remains controversial: it could be a bystander (ie, a marker of disease severity) effect or a pathogen with independent morbidity and mortality.[17,18] Reactivation of HSV is the first step before HSV-associated bronchopneumonitis, which can worsen lung inflammation or injury and pave the way for nosocomial bacterial pneumonia, thereby prolonging mechanical ventilation.[2,19]

Research on HSV reactivation and its prognosis has been published[4]; however, to our knowledge, Tuxen et al[8] conducted the only randomized, double-blind, placebo-controlled trial on acyclovir efficacy against HSV reactivation. They randomized 45 patients with acute respiratory distress syndrome to receive prophylactic acyclovir or placebo and found that acyclovir was associated with significantly less HSV reactivation (6% vs 71%, $P < .001$), but not with shorter mechanical ventilation durations or lower mortality. Because some

Table 3. Outcomes

Parameter	Study Group		P Value
	Acyclovir (n = 119)	Placebo (n = 119)	
Primary outcome			
Ventilator-free days at day 60, median (IQR)	35 (0-53)	36 (0-50)	.17
Secondary outcomes post randomization			
Day 60 mortality, No. (%)	26 (22)	39 (33)	.06
Duration of MV, median (IQR)	17 (7-30)	13 (7-23)	.41
Probability of more favorable outcome, %[a]	50.78	40.48	.16
ICU length of stay, median (IQR)	20 (12-41)	17 (11-31)	.10
HSV bronchopneumonitis, No. (%)	1 (1)	4 (3)	.37
Cytomegalovirus infection, No. (%)	1 (1)	5 (4)	.21
Hospital-acquired bacterial pneumonia, No. (%)	58 (49)	53 (45)	.52
Secondary bacteremia or fungemia, No. (%)	29 (24)	27 (23)	.75
ARDS postrandomization, No. (%)[b]	14 (12)	7 (6)	
Mild	2	0	
Moderate	7	2	.11
Severe	5	4	
Septic shock post randomization, No. (%)	22 (18)	27 (23)	.42
No. of days with study drug, median (IQR)	14 (11-14)	14 (10-14)	.69

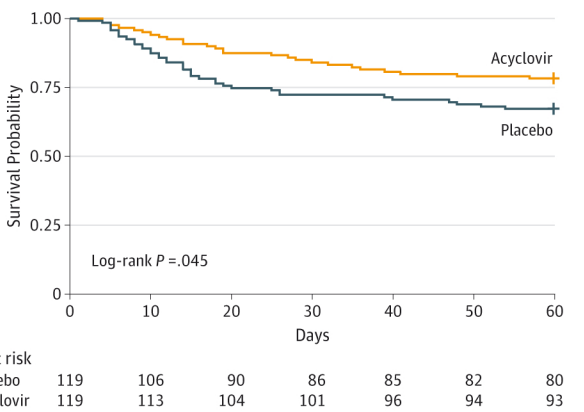
Abbreviations: ARDS, acute respiratory distress syndrome; HSV, herpes simplex virus; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation; Pao_2/FiO_2 (fraction of inspired oxygen) partial oxygen pressure in arterial blood/fraction of inspired oxygen ratio; PEEP positive end-expiratory pressure.

[a] Probability of more favorable outcome is a ranked composite incorporating death and days free from mechanical ventilation among survivors. It represents the estimated probability that an individual randomly selected from 1 treatment group will have a higher score (more favorable outcome) than an individual randomly selected from the other group. It is mathematically equivalent to the area under the receiver operating characteristic curve for the Mann-Whitney test. A value of 50% indicates no difference between groups.[13]

[b] The Berlin definition of ARDS is as follows: mild: Pao_2/FiO_2 greater than 200 but 300 or less, with positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) 5 cm H_2O or more; moderate: Pao_2/Fi_{O2} greater than 100 but 200 or less, with PEEP or CPAP 5 cm H_2O or more; severe: Pao_2/FiO_2 100 or less with PEEP 5 cm H_2O or more.[14]

patients, even those who are HSV seropositive, will never experience virus reactivation during their ICU stays, this prophylactic strategy of treating before reactivation may unnecessarily expose patients to acyclovir. Because of renal and neurologic toxic effects,[20,21] the applicability of prophylactic acyclovir may be questionable. Luyt et al[2] compared 42 ICU patients who developed HSV bronchopneumonitis—19 patients given acyclovir, 10 mg/kg, 3 times per day for 5 to 14 days and 23 patients without antiviral treatment. The investigators found that the clinical courses of all patients were similar, including hospital mortality rates (acyclovir, 37%; control, 57%). However, the criteria for treating patients with acyclovir were not defined by the authors. Although treating only patients with documented HSV bronchopneumonitis has the advantage of limiting acyclovir exposure to patients with true disease, it raises several issues, including a complicated definition of disease.[2] In addition, Traen et al[19] retrospectively analyzed 212 patients with HSV-1-positive respiratory tract or bronchoalveolar lavage-fluid cultures and compared the outcomes of acyclovir recipients (n = 106) vs those not given the drug (n = 106). Acyclovir was associated with lower in-ICU and in-hospital mortality rates, even after adjustment in multivariable Cox or propensity-score analyses. However, that analysis was retrospective and, despite adjustment, potential confounders might not have been taken into account (notably, the decision to administer acyclovir based on unknown criteria).

Figure 2. Survival Analysis Through 60 Days



Survival estimates in the intention-to-treat population.

To our knowledge, no published study has evaluated the effect of a preemptive strategy for ICU patients with HSV reactivation. Such a strategy has several advantages. First, acyclovir is given only to patients with HSV reactivation, therefore, not exposing those without reactivation to this potentially toxic drug. Second, patients are treated before lung disease occurs, and some authors have suggested that HSV might induce lung injury, paving the way for bacterial infection.[2,17] This kind of strategy is applied successfully for CMV in solid-

organ recipients; preemptive treatment of CMV reactivation seems to be, at least for some transplanted organs, noninferior to a prophylactic approach.[22] However, use of preemptive treatment implies implementing regular screening of patients susceptible to HSV reactivation.

We were unable to demonstrate any beneficial effect of acyclovir in ICU patients. This result could have been due to a lack of power of our study. As indicated above, some investigators have postulated that acyclovir could improve the prognosis of ICU patients having reactivated HSV by limiting the bronchioalveolar damage secondary to viral infection, and/or by preventing CMV replication, even the anti-CMV effect of acyclovir is usually observed with higher doses than the ones used in our study.[1,2,4,17] Although the acyclovir group had a nonsignificant lower day 60 mortality, the number of ventilator-free days was comparable to that of placebo-treated patients, implying that survivors in the acyclovir group had a longer mechanical ventilation duration (ie, fewer ventilator-free days) than the placebo recipient survivors. This longer duration of mechanical ventilation in acyclovir survivors might be due to the higher number of patients with extracorporeal membrane oxygenation support and the higher percentage of patients developing acute respiratory distress syndrome after randomization. Whether acyclovir could improve the survival of mechanically ventilated patients with reactivated HSV at the cost of a prolonged mechanical ventilation duration is unknown and remains to be explored. Whether targeting a more narrowly defined population (ie, patients with <2 organ failures) might have changed our results also remains to be determined.

Limitations

One major limitation of our study was the lack of serial monitoring of HSV shedding in respiratory tract secretions. It is known that HSV reactivation begins in the throat within the first 10 days of mechanical ventilation,[1] followed by a descending contamination of the bronchial tree. Using quantitative real-time polymerase chain reaction testing for the quantitative detection of HSV DNA, De Vos et al[23] described the time-course of HSV shedding in lower respiratory tract secretions and found that HSV emerged in tracheal and bronchial aspirates after a median of 7 (IQR, 5-11 days) days of intubation, followed by an exponential increase to reach very high HSV peaks (10^6-10^{10} copies/mL) in 78% of the HSV DNA-positive patients.[24] Therefore, although we cannot exclude that patients with HSV oropharyngeal reactivation could evolve toward a rapid, spontaneous resolution of HSV reactivation without acyclovir, this resolution appears to be uncommon in ICU patients requiring prolonged mechanical ventilation. Conversely, we cannot be sure whether acyclovir, 5 mg/kg, 3 times daily was able to stop virus reactivation and prevent lower respiratory tract colonization and/or infection in our study, although this dose has been shown to be effective to prevent HSV reactivation in a previous randomized clinical trial.[8]

Our study has other limitations. First, whether the study population and standard of care in the ICUs that participated in the Preemptive Treatment for Herpesviridae trial were similar to those observed elsewhere could be debatable. However, patients' clinical characteristics in our study were comparable to those reported in a large, nonselected database of patients who were mechanically ventilated.[25] Second, although our treatment groups did not differ significantly, acyclovir recipients received slightly more frequent, but not statistically significant, extracorporeal membrane oxygenation support and renal replacement therapy at randomization, and more developed acute respiratory tract distress syndrome post randomization, it remains unknown whether those findings could have affected the results. Third, using ventilator-free days as the primary outcome may be debated.[24] Fourth, we cannot exclude the possibility that some patients may have had HSV viremia or HSV organ disease without previous oropharyngeal reactivation and that we could have missed these patients. In addition, our primary hypothesis (8-day increase of ventilator-free days) was perhaps too optimistic, and our sample size may have limited the study's ability to detect a true effect.

Conclusions

It appears that for ICU patients with HSV reactivation in the throat while receiving mechanical ventilation for 96 hours or more, acyclovir, 5 mg/kg, 3 times daily compared with placebo was unable to increase the day 60 number of ventilator-free days.

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