Preemptive acyclovir to prevent herpes simplex virus bronchopneumonitis in mechanically ventilated patients with herpes simplex virus oropharyngeal reactivation: An ancillary study of the preemptive treatment for herpesviridae trial

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Abstract

Background: To evaluate the impact of preemptive acyclovir treatment on herpes simplex virus (HSV) bronchopneumonitis in mechanically ventilated patients with HSV oropharyngeal reactivation.

Methods: Ancillary study of the Preemptive Treatment for Herpesviridae (PTH) clinical trial. Patients included in that trial from one centre (Pitié-Salpêtrière Hospital) and in whom at least one bronchoalveolar lavage (BAL) was performed for ventilator-associated pneumonia suspicion were included in the present study. Rate of HSV bronchopneumonitis, defined as clinical symptoms suggesting pneumonia and presence of HSV in BAL fluid ≥10⁵ copies of HSV/10⁶ cells, were compared in patients who received either acyclovir or placebo.

Results: Eighty-three patients were included; 40 having received preemptive acyclovir and 43 having received a placebo, without differences between groups at admission or at randomization. The number of patients who developed HSV bronchopneumonitis was lower among acyclovir-treated patients than among placebo-treated patients (40% vs. 72%, respectively, p = .003). Results were similar when restricted to patients without HSV detected in the lower respiratory tract at randomization (31% vs. 61%, respectively, p = .03).

Conclusions: Preemptive acyclovir treatment in mechanically ventilated patients with HSV oropharyngeal reactivation reduces HSV bronchopneumonitis rate.

Keywords
Herpes simplex virus, bronchopneumonitis, acyclovir, ventilator-associated pneumonia

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Introduction

In the recently published Preemptive Treatment for Herpesviridae (PTH) trial, preemptive use of acyclovir for mechanically ventilated (MV) patients with oropharyngeal herpes simplex virus (HSV) reactivation failed to demonstrate a positive impact on day-60 ventilator-free days (VFDs), although a trend towards lower day-60 mortality rate was found in patients treated with acyclovir as compared to those having received placebo. Those results could be explained by the lack of acyclovir effectiveness, lack of HSV pathogenicity in MV patients, wrong outcome choice (day-60 mortality rate being more accurate than day-60 VFDs) or inability of acyclovir to prevent HSV bronchopneumonitis. Indeed, the rate of HSV bronchopneumonitis was similar in the two groups. Although the morbidity of HSV reactivation in the lower respiratory tract (and therefore its treatment) may be disputable, HSV bronchopneumonitis, that is, lung parenchyma involvement, is associated with potentially increased morbidity and/or mortality. HSV bronchopneumonitis is defined by clinical signs suggesting of pneumonia, presence of HSV in the lower respiratory tract and histological criteria, that is, HSV-specific nuclear inclusions in cells collected during bronchoalveolar lavage (BAL). However, the detection of those inclusions are subjected to intra- and inter-observer variability, may be difficult to search and frequently missed. The use of virus load in BAL fluid has been described as a surrogate of histology: a cut-off of 10^5 copies of HSV/10^6 cells had a good accuracy to predict HSV bronchopneumonitis and was associated with prognosis. In the recent PTH trial, the authors only used the historical definition for HSV bronchopneumonitis diagnosis and therefore may have underdiagnosed some episodes.

We therefore performed this retrospective study to evaluate, within the PTH trial, the impact of preemptive acyclovir treatment on HSV bronchopneumonitis in patients with HSV oropharyngeal reactivation, HSV bronchopneumonitis being defined by clinical symptoms suggesting of pneumonia and the presence of HSV in BAL fluid ≥10^5 copies of HSV/10^6 cells.

Methods

All patients included in the PTH trial in one participating centre (Pitié-Salpêtrière hospital) were retrospectively reviewed and included. The PTH trial, a double-blind, placebo-controlled, randomised study was designed to evaluate the impact of preemptive acyclovir, given intravenously at a dose of 15 mg/kg/day during 14 days, on MV duration, assessed by the number of days alive and free from MV at day 60 (MV-free days). Results of this study have been published elsewhere. Patients randomized in the study and suspected of having developed ventilator-associated pneumonia (VAP) underwent fiberoptic bronchoscopy and BAL. BAL fluid was sent to the bacteriological lab for bacterial culture and susceptibility testing, and to the virology lab for virus testing. In this, latter were tested for HSV genome and albumin gene were quantified using in-house real-time polymerase chain reactions (PCRs), as previously described, and HSV load was calculated and expressed in copies of HSV/10^6 cells collected by BAL. In patients with multiple episodes of VAP suspicion, BAL was repeated as frequently as needed. We retrospectively defined HSV bronchopneumonitis as VAP suspicion plus HSV load in BAL ≥10^5 copies of HSV/10^6 cells. Rate of HSV bronchopneumonitis were compared in both groups (acyclovir-treated and placebo-treated).

Ethics

The PTH trial was approved by an independent ethics committee (Comité de Protection des Personnes Sud Mediterranée 5).

Results

Among the 239 patients included in the PTH trial, 99 were included in Pitie-Salpetriere Hospital, and 83 had at least one episode of VAP suspicion that led to fiberoptic bronchoscopy and BAL analysis. Those 83 patients constituted the study population: 60 (72%) were males; their median (IQR) age was 56 (46-67) years, their simplified acute physiology score (SAPS) II and sequential organ failure assessment (SOFA) scores at intensive care unit (ICU) admission were 44 (35–56) and 10 (7–13), respectively. Their median (IQR) MV duration before randomisation was 9 (7–11) days, and 34 (41%) had HSV-positive BAL fluid at randomisation (patients having BAL in a time window from 48 h before to 48 h after randomisation and whose BAL was positive for HSV were considered as positive at randomisation). Characteristics of patients according to their randomisation arm (40 randomised in the acyclovir arm and 43 in the placebo arm) at ICU admission and at randomisation are displayed in Table 1. There were no differences between groups.

Outcomes

Virological outcomes are displayed in Table 1. Patients having received preemptive acyclovir developed less frequently HSV bronchopneumonitis than those having received a placebo, and their peak of HSV load in the BAL fluid was lower than the peak for patients having received a placebo. Ventilator-free days at day 60 and day-60 mortality rates were similar in both groups.
Since having HSV reactivation in the respiratory tract at randomisation may have an impact on HSV bronchopneumonitis rate, we separately analysed the 49 patients without HSV in the lower respiratory tract at randomization (26 in the acyclovir arm and 23 in the placebo arm). Their characteristics at ICU admission and randomisation were similar (Table 1). The rate of HSV bronchopneumonitis was lower in patients having received acyclovir, as compared to placebo, as well as their highest HSV load in BAL fluid (Table 1). Mortality rate and day-60 ventilator-free days were not different, although trend towards higher ventilator-free days was observed in the acyclovir-treated patients.

Interestingly, 40% of patients having received acyclovir (31% of those without HSV in the lower respiratory tract at randomisation) developed HSV bronchopneumonitis despite this treatment (Table 1).

### Discussion

In this ancillary study of the PTH trial, we found that acyclovir, given as preemptive treatment in patients with HSV oropharyngeal reactivation, allowed to reduce the incidence of HSV bronchopneumonitis. Moreover, although we were unable to show any significant effect on outcome, there was a trend toward higher number of MV-free days in the subgroup of patients without HSV reactivation in the lower respiratory tract at randomisation and treated with acyclovir. Since HSV bronchopneumonitis may be deleterious, this decrease in its incidence might explain, at least in part, the non-significant difference in mortality rates observed in the PTH trial. However, the use of acyclovir at a dosing of 15 mg/kg/day during 14 days did not suppress the risk of developing HSV bronchopneumonitis. Whether higher dose and/or prolonged duration of treatment may be more efficient remains to be determined.
Limitations of our work include the limited number of patients and the inclusion of only patients from one centre. Moreover, 16 patients included in the PTH study had no BAL and were therefore not included in the present ancillary study. However, it is unlikely that those patients developed HSV bronchopneumonitis; they were not sampled because they had no signs suggestive of pneumonia, which defines HSV bronchopneumonitis.4

Conclusion

In conclusion, preemptive use of intravenous acyclovir, at a dosing of 15 mg/kg/day during 14 days, in mechanically ventilated patients with HSV oropharyngeal reactivation, may reduce the frequency of HSV bronchopneumonitis. Whether this decrease has an impact on outcome remains to be determined.

Authors contribution

AT and CEL conceived and designed the study, performed the analysis and wrote the first draft of the manuscript. SB, OB and DB performed the virological analysis. AT, MPdC, MS, NB, GH, AC and CEL included the patients. All authors made significant contribution, read and approved the manuscript.

Declaration of conflicting interests

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Disclosure

DB reports having receiving fees from Biomérieux, Faron, Carmat, Aerogen, Merck Sharp and Dohme, outside the submitted work.

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