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CORRECTION

Correction to: Comparison of 8 versus 15 days of antibiotic therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia in adults: a randomized, controlled, open-label trial

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In this article, a few mistakes have been corrected and a few sentences have been changed in the abstract, in the take-home message, and in the text. Finally, there was a mistake in Supplementary file 2; it has now been replaced with the correct file. The authors apologize for these mistakes. The original article has been corrected.

Abstract

Purpose: Duration of antibiotic therapy for ventilator-associated pneumonia (VAP) due to non-fermenting Gram-negative bacilli (NF-GNB), including *Pseudomonas aeruginosa* (PA) remains uncertain. We aimed to assess the non-inferiority of a short duration of antibiotics (8 days) vs. prolonged antibiotic therapy (15 days) in VAP due to PA (PA-VAP).

Methods: We conducted a nationwide, randomized, open-labeled, multicenter, non-inferiority trial to evaluate optimal duration of antibiotic treatment in PA-VAP. Eligible patients were adults with diagnosis of PA-VAP and randomly assigned in 1:1 ratio to receive a short-duration treatment (8 days) or a long-duration treatment (15 days). A prespecified analysis was used to assess a composite endpoint combining mortality and PA-VAP recurrence rate during hospitalization in the intensive care unit (ICU) within 90 days.

Results: The study was stopped after 24 months due to the slow inclusion rate. In intention-to-treat population (n = 186), the percentage of patients who reached the composite endpoint was 25.5% (N = 25/98) in the 15-day group versus 35.2% (N = 31/88) in the 8-day group (difference 9.7%, 90% confidence interval (CI) − 1.9%–21.2%). The percentage of recurrence of PA-VAP during the ICU stay was 9.2% in the 15-day group versus 17% in the 8-day group. The two groups had similar median days of mechanical ventilation, of ICU stay, number of extra pulmonary infections and acquisition of multidrug-resistant (MDR) pathogens during ICU stay.

Conclusions: Our study failed to show the non-inferiority of a short duration of antibiotics in the treatment of

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PA-VAP, compared to a long duration. The short duration strategy may be associated to an increase of PA-VAP recurrence. However, the lack of power limits the interpretation of this study.

Take-home message

The optimal duration of treatment for *Pseudomonas aeruginosa* ventilator-associated pneumonia remains unknown. In a prospective randomized trial, we did not demonstrate the non-inferiority of a short duration (8 days) of antibiotic therapy.

Results

Patients

Between June 3rd 2016 and May 22nd 2018, 196 patients were enrolled in 30 centers between June 2016 and May 2018, of whom 190 underwent randomization. The study was stopped after 24 months due to the slow inclusion rate. Indeed, it was estimated that it would have taken 6 years to enroll the 600 patients needed to demonstrate the non-inferiority on the composite endpoint. Two patients refused their participation, and two patients were under guardianship, resulting in an ITT analysis of 186 patients. After excluding 34 patients with major deviation to the protocol (patients wrongly included (n = 32) and randomization not respected (n = 2), the PP population included 152 patients (Fig. 1). Reasons for wrong inclusions are detailed in the Supplementary file 1. In the overall population, the patients were mostly male (75.8%), aged of 59.4 ± 17.4 years and with a medical history of hypertension (25.3%). The first diagnoses at ICU admission were acute circulatory failure for 41 patients (22%), acute respiratory failure for 35 patients (18.8%) and trauma for 35 patients (18.8%). Baseline characteristics are reported in Table 1.

Primary and secondary outcomes

In the ITT population, 25 (25.5%) patients of the 15-day group and 31 (35.2%) patients of the 8-day group had a PA-VAP recurrence or were dead in ICU at 90-day (Table 2, Fig. 2). The non-inferiority of 8-day group compared to the 15-day group was not demonstrated (difference 9.7%, 90% CI − 1.9 to 21.2%), considering the upper bound of the 90% CI of the difference being greater than 10%, similar to the analysis performed on the PP population (n = 152, difference 12.8%, 90% CI 0.4–25.6%). Considering a clinically relevant difference between groups at baseline on heart failure, hypertension, administration of catecholamines and PaO_2/ FiO_2 ratio, a post hoc analysis adjusted on these variables was performed, taking into account the center as random effect. Previous results were confirmed with an adjusted difference in the ITT population of 12.5% (90% CI 1.3–23.6%), similar to the analysis performed on the PP population 16.3% (90% CI 3.9–28.8%). The 90-day overall survival rate in the 15-day group and in the 8-day group were comparable (81.4%, 90% CI 73.8–87% and 75.6%, 90% CI 66.9–82.3% respectively, HR = 1.37, 90% CI 0.81–2.33) (Supp. Figure 1). There was a trend toward a higher proportion (almost twice) of recurrence PA-VAP during the ICU stay in the 8-day compared to the 15-day group (17% versus 9.2%, difference 7.9%, 90% CI -0.5–16.8%). The Fine and Gray model showed a higher risk of recurrence of PA-VAP in the 8-day group compared to the 15-day group (sHR 1.99, CI 90% 1.01–3.95) (Supp. Figure 2). The 15-day and 8-day groups had similar median in duration of mechanical ventilation (25 (15.5–35) versus 22 (12–41)), duration of ICU stay (34 (23–56) versus 34 (20–54)), number of extra-pulmonary infections (1 (0–2) versus 1 (0–2)) and similar proportion of MDR pathogens acquisition during ICU stay (24.7 versus 20.2%) (Table 3). As expected, the median exposure to antibiotics was higher in the 15-day group compared to the 8-day group, respectively 23 days (15–34) versus 18 days (11.5–28.5), difference − 5% (95% CI − 9 to 0%).

Discussion

In this prospective randomized controlled trial, non-inferiority of a short duration strategy (8 days) compared to a long duration strategy (15 days) for the composite endpoint of mortality and PA-VAP recurrence occurring during hospitalization in the ICU within 90 days was not demonstrated in adult patients with PA-VAP.

Moreover, the patients in the 8-day group were twice as likely to have a PA-VAP recurrence as those in the 15-day group. Furthermore, the Fine and Gray model show a higher risk of PA-VAP recurrence considering the competing risk of death in 8-day group versus 15-day group. While patients in the 8-day group were indeed less exposed to antibiotics during the ICU stay, we did not find more multidrug-resistant pathogen acquisition in the 15-day group. Although antibiotic duration for the treatment of VAP remains a challenge, only few randomized controlled trials have addressed this issue. Two studies compared 8 vs. 15 days of antibiotic durations [5, 13], two others compared 7 vs. 10 days [14, 15] and one study compared 8 vs. 12 days [16]. Two published systematic reviews found no difference between short and long durations of antibiotic therapy with regard to day-28 mortality [6], duration of mechanical ventilation or length of ICU stay [6, 17]. However, in the subset of patients with non-fermenting Gram-negative bacteria, there was a trend toward lower recurrence for

the long-duration arms. In the study conducted by Capellier et al. [13], focusing on early-onset VAP, the rate of secondary infection was higher in the 8-day group than the 15-day group. In the PneumA study, patients with VAP caused by NF-GNB treated for 8 days had a higher recurrence-infection rate (40.6% versus 25.4%). Finally, among 274 patients with late-onset VAP, a randomized controlled trial shown that a 7-day course was found to have non-significant higher rates of clinical failure and 28-day mortality compared to a fixed 10-day course [15]. In our trial, the percentage of patients who died or had a recurrence of PA-VAP was 35.2% in the 7-day group (ITT population), close to the mortality and/or recurrence of PA-VAP rate of 35.7% observed by Planquette et al. in a retrospective study of 393 PA-VAP [11] in which the median antibiotic duration in survivors was 9 days (IQR, 6–12). Despite a higher recurrence rate, the short-duration strategy was not associated with an increased mortality, a longer duration of mechanical ventilation or length of ICU stay in our study. Thus, more research seems needed before any definitive conclusions about the best duration of antibiotic therapy for VAP due to non-fermenting GNB can be drawn. A duration of 8 days of treatment cannot be ruled out but our findings invite to a prudent approach based on a close clinical and biological monitoring, although this was not tested in our study. Biomarkers could be assessed to monitor specifically the duration of treatment in this setting. To our knowledge, this study is the first randomized controlled trial specifically focused on PA-VAP. In our trial, the expected incidences of components of primary outcome were correctly estimated: the percentage of patients who died or had a recurrence of PA-VAP was 27.5% in the 15-day group and 40.3% in the 8-day group. These proportions are in agreement with results of available studies [17]. Protocol of planned antibiotic durations has been fully respected with median duration of 15 and 8 days in 15-day and 8-day groups, respectively, and as expected. Compliance with the planned duration of antibiotic therapy was acceptable (around 80%) (see Supplemental Table 2). The main limitation is that the study ultimately only 33% of the patients initially planned despite the participation of 30 centers throughout France, including medical, surgical and general intensive care units in university and non-university hospitals. Indeed, because of the late onset of PA-VAP during the ICU stay, many patients were already included in other interventional studies and as such could not be included in our trial. A post hoc sensitivity Bayesian analysis suggests that the probability of non-inferiority was close to 55% in the ITT population and 40% in the PP population (Supplementary File 2).

In conclusion, our trial did not demonstrate non-inferiority of 8 days duration of antibiotic therapy compared to 15 days, due to a higher number of recurrences.

Supplementary Information
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