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LETTER

Impact of macrolide therapy in critically ill patients with acute respiratory failure: a desirability of outcome ranking analysis to investigate the OUTCOMEREA database

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Dear Editor,

There is substantial evidence that macrolides exhibit immunosuppressive properties, in addition to their antimicrobial effect [1]. In patients with acute respiratory failure (ARF), studies with small sample sizes have suggested that macrolide therapy may have some beneficial effects owing to their immunomodulatory properties rather than their antimicrobial effect [2, 3]. Indeed, authors found an association between macrolide therapy and decreased mortality or shorter duration of mechanical ventilation in patients with ARF [2–4].

To test the following hypotheses, namely whether macrolides decrease mortality, mechanical ventilation duration, or impact the risk of secondary infections within 28 days following the intensive care unit (ICU) admission in patients with ARF, we conducted an observational retrospective cohort study from the French prospective multicenter OUTCOMEREA database (20 ICUs from 1997 to 2015). Adult critically ill patients admitted to ICU for ARF or developing ARF within 48 h following the ICU admission and hospitalized for at least 4 days in ICU were included in the study. Patients were divided into two groups: those who received macrolides within 3 days after ICU admission and those who did not receive macrolides. The analysis was performed using the desirability of outcome ranking (DOOR) approach (ESM 1). All analyses were adjusted for confounding factors using inverse probability of treatment weighting (IPTW).

Of the 22,125 patients admitted to ICU during the study period, 7182 met the inclusion criteria; among them, 1295 received macrolides within 3 days after ICU admission and 5887 did not (Supplemental Fig. 1 and Supplemental Table E1). Macrolide therapy was administered in all patients either for its antimicrobial property ($n=1250$) or for its promotility effect in upper gastrointestinal bleeding ($n=45$). The median [IQR] duration of macrolide therapy was 3 days [2, 6]. Confounding risk factors for macrolides administration within 3 days after ICU admission included in the IPTW model are described in Supplemental Table E2. The IPTW-adjusted probability of a better outcome (death and secondary infection acquisition) was 51% (95% CI 48.9–53.2%) in the macrolides group. The IPTW-adjusted probability of a better outcome (death and mechanical ventilation duration) within 28 days after ICU admission in the macrolides group was 49.4% (95% CI 46.8–51.6%) (Supplemental Table E3). The confidence interval of the probability contains 50% indicating the absence of benefit of macrolides. Figure 1 displays the disposition over time of IPTW-adjusted mortality and secondary infection acquisition within 28 days following the ICU admission in both groups.

While DOOR has been developed for assessing desirability of outcome in interventional studies, our results confirm its possible use to investigate observational studies [5]. Thus, our findings do not support any association between macrolide therapy and survival, decreased

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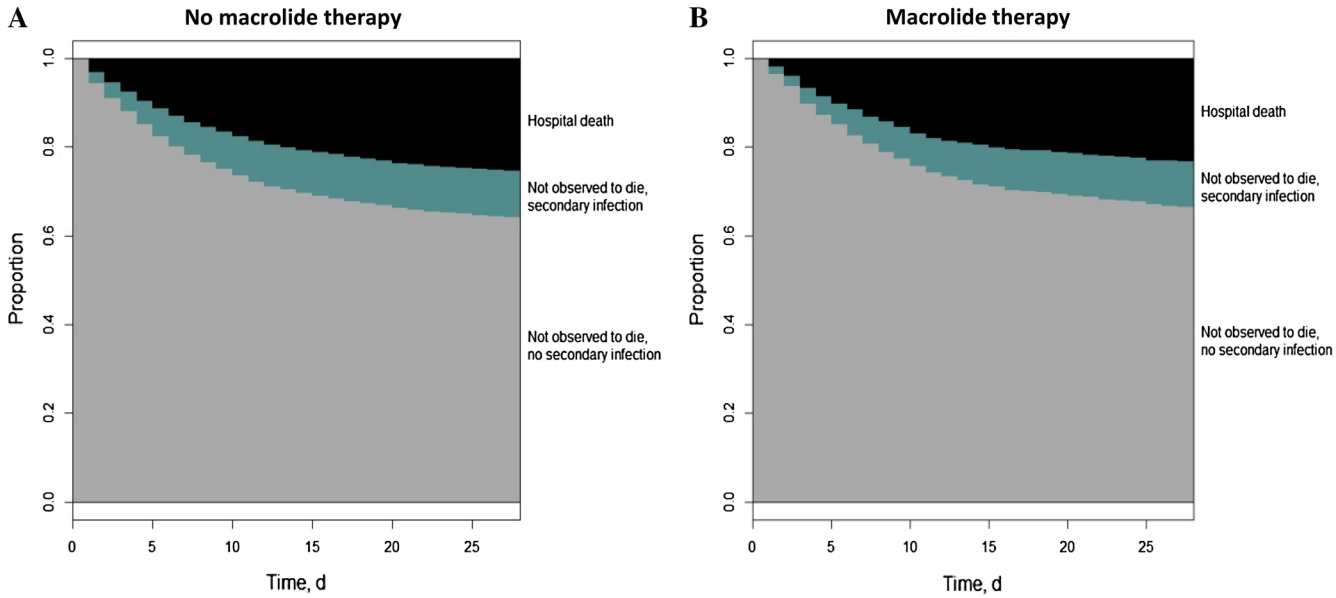

Fig. 1 Disposition over time of inverse probability of treatment weighting-adjusted mortality and secondary infection acquisition within 28 days following the intensive care unit (ICU) admission ($n = 7182$). **a** No macrolide therapy within 3 days after ICU admission ($n = 5887$). **b** Macrolide therapy within 3 days after ICU admission ($n = 1295$)

mechanical ventilation duration, or secondary infection acquisition in critically ill patients with ARF. However, differences in time and dose of macrolides may explain discrepancies between our results and previous studies. Moreover, other unidentified confounding factors might have been overlooked. Finally, the results may be influenced by the arbitrariness in the number of categories selected in the DOOR analysis. Advances in understanding the interactions between macrolides and the host immune system may help to identify ARF patients who may benefit from or may be affected by macrolide therapy.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05586-1) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standard statement
These retrospective analyses of a prospective observational study were exempt from approval per the institutional review board or local ethics committee. In accordance with French legislation on non-interventional studies, the need for signed informed consent from the participants was waived. However, the patients and their next of kin were asked whether they were willing to participate in the database.

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