

CORRESPONDENCE

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The impact of extracorporeal membrane oxygenation on the exposure to isavuconazole: a plea for thorough pharmacokinetic evaluation

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Extracorporeal membrane oxygenation (ECMO) is increasingly used to provide temporary (cardio)pulmonary support in patients with life-threatening respiratory and/or cardiac failure, including critically ill patients with influenza- and coronavirus disease 2019 (COVID-19)-associated acute respiratory distress syndrome. Critically ill patients often exhibit altered and variable pharmacokinetics (PK) of antimicrobials owing to pathophysiological alterations (e.g., fluid shifts, hypoalbuminemia, renal dysfunction and augmented renal clearance) and extracorporeal treatments. ECMO might significantly affect the PK of drugs due to hemodilution from circuit priming and drug sequestration in the ECMO circuit. The impact of ECMO on the PK of mold-active triazoles, such as voriconazole and isavuconazole, has become increasingly important as they are recommended as (first-line) anti-fungal therapies for influenza- and COVID-19-associated pulmonary aspergillosis. Based on the high lipophilicity and extensive plasma protein binding of isavuconazole, the triazole is theoretically prone to adsorption to ECMO circuits and subsequent reduction in plasma concentrations. To date, isavuconazole exposure in ECMO patients

has only been documented in two case reports and a case series ($n=3$) in which reduced plasma concentrations during ECMO have been suggested [1–3]. In this correspondence, we would like to emphasize that the suggestion of reduced isavuconazole exposure due to ECMO *as such* should be interpreted cautiously and that additional studies are needed to evaluate the independent impact of ECMO on the PK of isavuconazole. This is in accordance with the mold-active triazoles voriconazole and posaconazole, for which drug sequestration into the ECMO circuit has been suggested by *ex vivo* studies and case reports. However, an independent effect of ECMO could not be confirmed in larger retrospective [4] or prospective studies [5].

We here report isavuconazole trough concentrations (C_{\min}), which were measured during routine care in four critically ill patients with concomitant isavuconazole and veno-venous ECMO treatment (approval from the local Ethics Committee; S65215). For each patient, information on ECMO and isavuconazole treatment is depicted in Fig. 1. Demographic and clinical characteristics are summarized in Additional file 1.

In our case series, isavuconazole exposure was highly variable and four C_{\min} were lower than 1 mg/L, which can be advocated as the minimum C_{\min} threshold, based on the European Committee on Antimicrobial Susceptibility Testing breakpoints for *Aspergillus fumigatus*, *A. flavus* and *A. terreus*. Multiple factors might contribute to the variability in isavuconazole C_{\min} , including administered

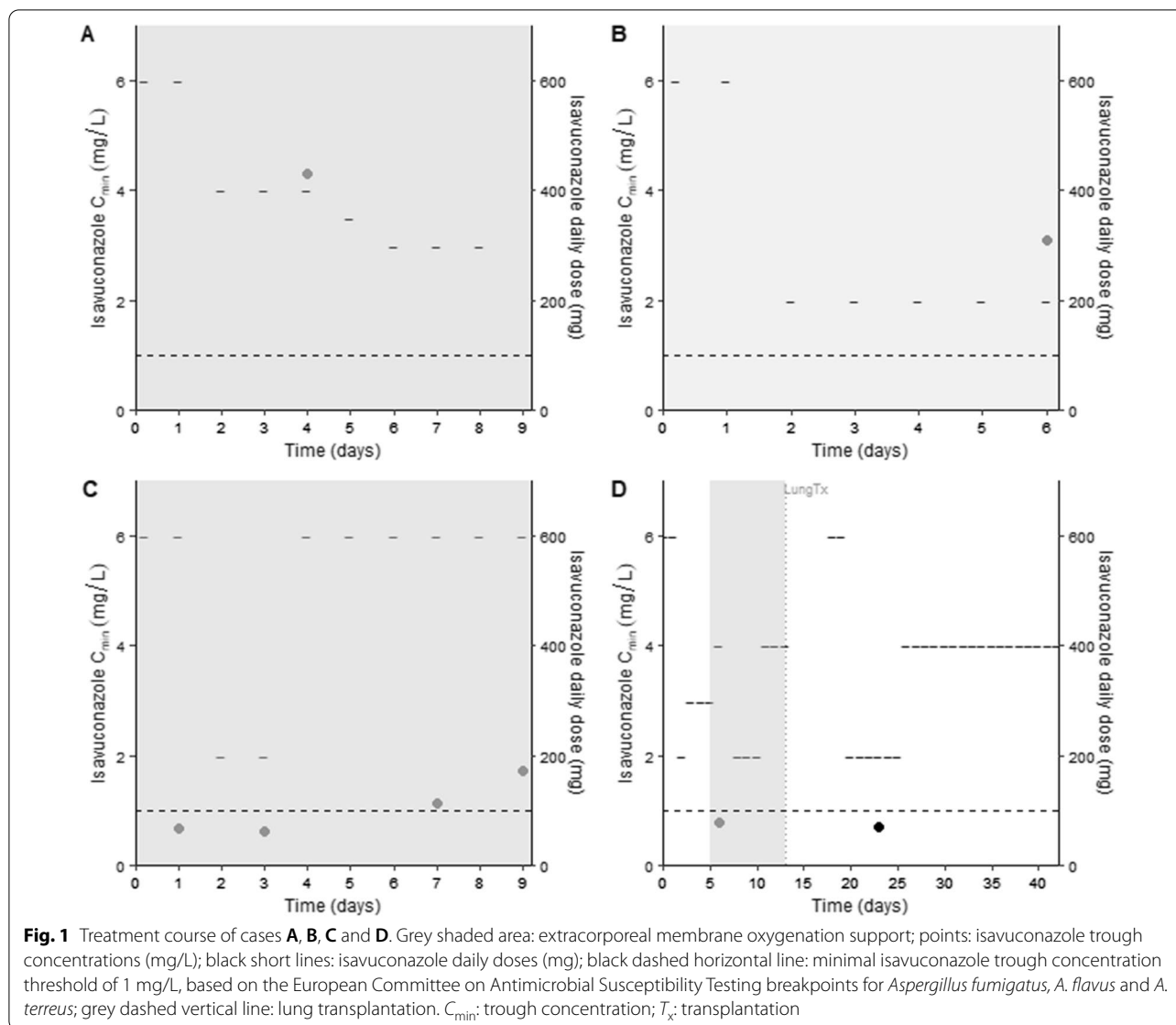
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doses, treatment duration and time needed to reach steady state after therapy initiation/dose adjustment. Dose-corrected C_{min} are presented in Additional file 1: file 2. The C_{min} in cases A and B suggest that adequate isavuconazole exposure can be achieved during ECMO support with a standard dosing regimen. In case A, a C_{min} of 4.3 mg/L was reached with an increased maintenance dose of 200 mg q12h. Considering the linear PK of isavuconazole, it could be hypothesized that a standard dose of 200 mg q24h would have resulted in a $C_{min} > 1$ mg/L. In case B, this minimal target C_{min} was achieved with a standard maintenance dose. In contrast, the isavuconazole C_{min} in cases C and D did not exceed the target of 1 mg/L when correcting for the standard maintenance dose of 200 mg q24h. The latter results are in line with

the previous reports by Zhao et al. [3] and Miller et al. [1], in which subtherapeutic exposure following a standard dosing regimen was documented and ascribed to ECMO *as such*.

Unfortunately, based on the previously published reports [1–3] and our case series, the independent impact of ECMO on isavuconazole exposure in critically ill patients cannot be assessed. Therefore, the key question whether subtherapeutic isavuconazole exposure in ECMO patients is caused by ECMO or by critical illness itself remains unanswered. This evidence gap underlines the need for large PK evaluations in critically ill patients, including those with augmented renal clearance, hypoalbuminemia, hepatic and renal dysfunction, renal replacement therapy and ECMO. Pending additional data (*e.g.*,

ICONIC study, ClinicalTrials.gov: NCT04777058), therapeutic drug monitoring of isavuconazole is warranted in critically ill patients, both in ECMO and non-ECMO patients.

Abbreviations

C_{min} : Trough concentration; ECMO: Extracorporeal membrane oxygenation; PK: Pharmacokinetic; T_x : Transplantation.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-022-04093-y>.

Additional file 1. file 1: Baseline characteristics of patients included in the retrospective analysis of isavuconazole trough concentrations during extracorporeal membrane oxygenation (n= 4). **file 2:** Ratio of isavuconazole trough concentrations to isavuconazole daily doses for patients concomitantly treated with isavuconazole and extracorporeal membrane oxygenation (n= 4).

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Author contributions

Conceptualization: BM, RVD, IS; methodology: BM, RVD, IS; investigation: BM, JW, YD, NVR, KD, PM, GH, CVDB, RVD, IS; Analysis: BM, RVD, IS; writing—original draft: BM, RVD, IS; writing—review and editing: JW, YD, NVR, KD, PM, GH, CVDB. All authors read and approved the final manuscript.

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Availability of data and materials

Individual participant data that underlie the results reported in this manuscript are available from the corresponding author upon reasonable request, providing the request meets the local ethical and research governance criteria after publication. Patient data will be anonymized and study documents will be redacted to protect the privacy of participants.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee Research UZ/KU Leuven (S65215). Not applicable.

Consent for publication

Not applicable.

Competing interests

JW reports investigator-initiated grants from Pfizer, Gilead and MSD; consulting fees from Pfizer and Gilead; speakers' fees from Pfizer, Gilead and MSD; travel fees from Pfizer, Gilead and MSD; participation in advisory boards of Pfizer and Gilead; receipt of study drugs from MSD, outside the submitted work. YD reports speakers' and travel fees from Pfizer and participation in advisory boards of Pfizer, outside the submitted work. GH is supported by the Flanders Research Foundation (FWO Vlaanderen) through a senior clinical research fellowship. IS is supported by the Clinical Research Fund of UZ Leuven and reports consulting fees from Pfizer and Cidara; speakers' fees from Pfizer; travel fees from Pfizer, outside the submitted work. BM, NVR, KD, PM, CVDB and RVD have no conflicts of interest to declare related to this work.

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