LETTER TO THE EDITOR

Author Reply: Therapeutic Drug Monitoring of Isavuconazole: Lessons Learnt from a Real-life Setting in a Tertiary Care Center in India

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Dear Editor,

We thank the authors for their knowledgeable comments on our study "Therapeutic drug monitoring (TDM) of isavuconazole: Lessons learned from a real-life setting in a Tertiary Care Center in India."

Isavuconazole has demonstrated good oral bioavailability and consistent levels, and hence the need for therapeutic drug monitoring has been challenged. The 2016 Practice Guidelines for the Diagnosis and Management of Aspergillosis published by the Infectious Diseases Society of America (IDSA) stated that more evidence is needed to determine whether TDM is helpful or necessary for isavuconazole.[1] However as shown in our study, 22% of the patients had their dose of isavuconazole changed after levels were ascertained. Hence, we want to add to the growing body of evidence that TDM for isavuconazole is useful and should be performed. Also, there is a need to generate local data, as it may be influenced by CYP3A4/5 polymorphisms.

We agree that critically ill patients may have reduced levels of isavuconazole, and critical illnesses may alter pharmacokinetics.[2] In fact, any illness may alter the levels, as levels measured in healthy volunteers and patients may be different from those obtained in patients.[3] We had 29 patients who were in the intensive care unit (ICU) at the time levels were drawn. In our study, ICU stay was not a significant factor associated with subtherapeutic levels. Hence while we agree that the determination of sequential organ failure assessment (SOFA) score will add merit to the study, and identify a subset of patients who will benefit more from TDM, our study was underpowered to look into this. As the authors have rightly stated, future studies to ascertain levels specifically in patients with high SOFA scores, and renal impairment are needed. Only one patient had a percutaneous endoscopic gastrostomy (PEG) tube, and he was found to have therapeutic levels. All patients included in our study were administered oral isavuconazole (we excluded those receiving IV isavuconazole), and this largely explains the very small number of patients having feeding tubes. This also explains the fact that none of the patients included in this study were on a ventilator. The primary intention was to analyze and generate real-world evidence on TDM for isavuconazole in the Indian setting. Again, we agree that larger studies are needed to ascertain levels in patients on renal replacement therapy, extracorporeal membrane oxygenation (ECMO), or those having nasogastric (NG) or PEG tubes. This would have a much wider implication for intensivists. However, these need to be powered sufficiently before arriving at conclusions which can change the practices in the ICU.

Overall, our study emphasizes the need for TDM for isavuconazole and adds to the growing evidence for the need to obtain drug levels. It also shows that isavuconazole is generally well tolerated. Factors associated with subtherapeutic levels of isavuconazole need to be assessed in larger studies to help identify those patients who are at risk for having subtherapeutic drug levels.

We appreciate the valuable comments from the authors and plan to conduct larger studies looking at these factors in the future after reading this insightful feedback.

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