Reviewer's report

Title: Evaluation of Intravenous Voriconazole in Patients with Compromised Renal Function

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Reviewer: Dionissios Neofytos

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This is a retrospective study on the use of IV voriconazole (VOR) in patients with underlying baseline renal impairment. While this study provides additional data to support using this formulation of VOR even in patients with creatinine clearance (CrCl) <50, I have the following suggestions for the authors.

1) My major problem with this study is that conclusions in the Abstract, Background, and Discussion should be less definitive, much less stronger in many parts of the manuscript. These are retrospective data and although supported by other recent reports, the authors should be cautious and be "less definitive" in the way they present their conclusions.

2) Background: 1st paragraph, "In the latter half ... tertiary care cancer centers [7,8]": this is too long if not redundant for the purposes of this manuscript. In addition, the statement that "a decrease in Aspergillus infections ... and voriconazole [5,6]" is not accurate. Data from single-center and multi-center cohorts suggest that the rates of Aspergillus infections, particularly in the transplant setting, have remained stable since the late 1990s.

3) Methods:
   (a) Were patients requiring hemodialysis or hemofiltration excluded?
   (b) RIFLE criteria: what grades of renal function worsening were used? RIFLE criteria specify three different degrees of renal function deterioration. The authors should also specify what they observed.

4) Results
   (a) Nephrotoxic agents: these should be presented in detail, for all groups, and if possible duration of administration
   (b) Duration of antifungal treatment is only presented as a mean in Table 1. What was the range, including the minimum duration of antifungal administration?
   (c) Voriconazole levels: were they drawn in any of these patients? What doses of voriconazole were administered? Loading doses were given to all patients?
   (d) What were the underlying diseases of these patients? Transplant (lung, kidney, bone marrow), hematologic malignancies, other? Were they neutropenic? What was the baseline liver function of these patients (considering that voriconazole is metabolized in the liver)?
(e) Fungal infections: it is not clear whether patients were colonized or infected with fungal pathogens. Formal definitions should be used and data presented in similar fashion. It is impossible to assess "underlying fungal disease" in Table 1 and in the text without knowing whether these were real infections or simply colonizing organisms.

(f) In the same context, it would be helpful to know if antifungal treatment was for prophylaxis vs. empirical vs. targeted.

(g) The logistic regression analysis results should be presented in a more organized and detailed fashion. I am confused as to which variables were included in these analyses. Site of infection was supposedly entered in the univariate analyses, but not specific IFI. However, it is reported that the "infecting organism" was the strongest predictor in the multivariate analysis. What did the univariate analyses show? What did the "infecting organism" represent (please see comment d)? This needs to be better clarified.

5) Discussion
(a) The second paragraph is not adding much to the Discussion.
(b) More recent data on the use of IV VOR in patients with renal dysfunction should be referenced in Discussion paragraph 4.
(c) It is intriguing that patients treated with fluconazole had worse renal function outcomes. As the authors discuss in the 5th paragraph, this may have to do with underlying status of these patients (e.g. were these patients more likely to have invasive candidiasis, hence did worse? were patients with Aspergillus "infections" simply colonized with this organism and not really infected? ).
(d) Under limitations, would add some of the above comments. Also, it is clear from Table 2 that patients on caspofungin and fluconazole had worse baseline renal function. Could it be that there was a selection bias and patients treated with IV VOR were not that sick, hence their renal dysfunction was not that bad compared to the other patient groups?

6) Figure 1: not needed
7) Figures 2a and b: is the x axis really "time to acute renal insufficiency"? All patients had renal insufficiency at baseline by definition. Re-name x axis.
8) Table 4: not needed.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have received research grants from Pfizer and have participated in advisory boards for Roche.