Author's response to reviews

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

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Author's response to reviews: see over
Editorial Board Comment:

*The manuscript by Lilly et al. has been extensively reviewed by three expert reviewers and there are some major points raised and described in detailed in each reviewer’s report. The authors should define the criteria used to assess comorbidity and renal function, as well as provide data on patient underlying diseases and details on the infecting (colonizing?) yeast or mould. I also agree with the reviewers’ suggestions on specifying the cases where treatment was empirical, prophylactic, or targeted and against which suspected or confirmed fungal pathogen. Studies as this are very useful and much needed. However, data on voriconazole doses administered and data on voriconazole levels would be extremely helpful if included in the manuscript.*

Response:

Thank you for the opportunity to respond to your and the Reviewers’ comments. Our responses to their comments are presented below in contrasting font (not italicized); the page numbers refer to the clean and not marked-up copy of the manuscript. With respect to your comments, comorbidity was assessed by the presence or absence of common diseases that are associated with renal dysfunction, specifically the presence of hypertension, diabetes mellitus, or nephropathy as presented in Table 1. Renal function (creatinine clearance) was assessed utilizing two estimations based upon the patient’s serum creatinine levels and age. One estimator, the Cockcroft-Gault equation, also included the patient’s actual body weight and gender. The other estimator, the Modification of Diet in Renal Disease (MDRD), also included gender and race in the calculations. We found that there were no statistically or clinically significant differences in the two estimators for each patient and as such, chose the more accepted and clinically used Cockcroft-Gault equation for our analyses. The dosing of antifungal agent was monitored by a clinical pharmacist and was in strict accord with the manufacturer’s recommendations as detailed in the FDA-approved package insert.
Reviewer #1 comments

The conclusions of the authors are not fully supported by the presented data. This is a retrospective, single center, observational study carrying all the limitations of such studies, as the authors acknowledge. The numbers of patients, especially those treated with voriconazole, are too low to jump to conclusions and make strong statements. Moreover, it seems that there is a selection bias: Patients were excluded from analyses if they had “unstable renal function” at baseline, assessed as a 50% difference in Scr or estimated Clcr on two measurements within 4 days of starting IV antifungal therapy. How do the authors know that the difference in Scr values is due to “unstable” renal function and not to the nephrotoxicity of the antifungal agent? How many patients were excluded using this criterion? On the other hand, patients eligible for analysis had been dosed for a minimum of 4 days of IV antifungal therapy and had serum creatinine (Scr) levels while on therapy and at the end of IV antifungal therapy. That means at least in some of these patients, differences of Scr levels on day 4 of AF Tx were attributed to the drug and not to “unstable” renal function. On what basis?

Response (page 12):

To address the issue of confounding by fluctuations in serum creatinine that were not due to the administration of an anti-fungal agent we excluded cases with unstable creatinine values in the four days before the antifungal agent was administered. We have modified the manuscript to make it more clear that the exclusion was before the initiation of antifungal therapy rather than after antifungal administration.

On table 1, underlying fungal disease has been diagnosed in only 9 (47%) of 19 pts on voriconazole. Probably the rest 10 patients received vori empirically for probable or possible IFI. On the contrary, a specific IFI has been diagnosed in 46 (83%) of 55 pts on caspofungin and 42 (77%) of 54 pts on fluconazole. These data contradict with the statement that a specific fungus is the major factor associated with renal deterioration. Interestingly, 3 patients with aspergillosis received fluconazole, which is not active against molds.

Response (page 5 and Table 1):

In accord with the comments of the reviewer, we have stratified the indications for therapy by antifungal agent and have modified the discussion to note that prophylactic voriconazole was used in patients with acute myelogenous leukemia. Due to the nature of the analyses that were performed, differences among the indications for antifungal treatment do not alter the validity of the association of the organism that was isolated with the development of renal dysfunction.
Moreover, patients receiving voriconazole had significantly better Scr and BUN values at baseline. Maybe the caring physicians preferred to give voriconazole only to patients with better Scr – BUN. It would be more meaningful to examine two subsets of patients: with moderate (creatinine clearance 30-50 mL/min) or severe (CrCl <30 mL/min) renal insufficiency.

Response (Table 3):
We agree with the reviewer and have performed additional analyses to address this important consideration. We calculated Max Scr, Lowest Clcr, ClEOT, % change in Clcr, and the assessment of renal dysfunction for each antifungal treatment group stratified by baseline Clcr (30 to 50 and < 30 mL/min) and placed our findings in the text and in Table 3 of the revised manuscript.

Regarding the concomitant nephrotoxic agents, there was one or more per patient? If some patients received more than one nephrotoxic agents, they were in greater risk for deterioration of renal function.

Response (page 5):
The Reviewer raises a very interesting and valid comment and we have provided more detail with regard to patients that received more than one nephrotoxin. It is well-established that drug-associated nephrotoxicity is more likely from two or more nephrotoxins compared with one nephrotoxin. We tabulated the number of patients receiving more than 1 concomitant nephrotoxin and added these data to the Results section. One could argue that the percentage of patients receiving multiple concomitant nephrotoxins in the voriconazole group (26%) compared with the other two treatment groups may have biased the findings against voriconazole. However, no greater decrement in renal function was found in the voriconazole treatment group, despite the imbalance of multiple concomitant nephrotoxic agents in this group.

One major drawback is that the underlying disease of the study patients is not mentioned. Patients in the ICU, with candidemia/sepsis, malignancy, and under chemotherapy are at greater risk for acute kidney injury.

Response (pages 5 and 9, Table 1):
We have performed additional studies to characterize the “underlying condition” of the patients. We agree that this information is of interest even though it was not expected to and did not appear to predict or confound renal outcomes. Accordingly we have modified the Results, Discussion, and Table 1.
All study patients had compromised renal function at baseline. What was the cause? Chronic renal failure due to diabetes or hypertension? Acute injury due to previous treatment? This clinical information is important to assess the effect of antifungals on further deterioration of renal function.

Response (Table 1):
We have modified Table 1 to make the frequency of hypertension, diabetes, and nephropathy more evident. These common diseases account for the majority of the observed baseline renal dysfunction, however, a substantial minority of patients with compromised renal function were exposed to nephrotoxic agents including NSAIDs which could account for some of these cases. Others did not have known causes for impaired baseline renal dysfunction. This information now appears in Table 1.

The only factor associated with AKI was the infecting organism. What was the organism associated with the greatest risk for AKI? It is not clear what the authors imply: candida vs. molds? Or specific candida species, such as C. glabrata or C. krusei, causing more severe disease?

Response (pages 9 and 11):
We agree with the Reviewer that identifying specific organisms would be of great interest, but are limited by the sample size from identifying candidal species that were more or less associated with poor renal outcomes. We have included this insightful hypothesis in the discussion section as a limitation to the study and request for additional studies to examine more thoroughly this association.

Although differences in 28-day mortality among the three treatment groups were not statistically significant, patients receiving voriconazole had higher mortality (42% vs. 26 vs. 29%). This reflects the differences in the severity of underlying diseases between the 3 study groups, making the results less interpretable. Authors should comment on it.

Response (page 9):
We have modified the discussion section to indicate that the differences in mortality may reflect differences in severity of the underlying diseases among the treatment groups that appears to be due in part to the use of prophylactic voriconazole for higher mortality risk patients with acute myelogenous leukemia.
Reviewer #2 comments

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.

Response (pages 9 – 11):
We have modified the manuscript and background to better present the limitations of this clinical practice study. We believe that targeting a high risk population and including all eligible cases from a clinical population gives us substantial insight into the risks of SBEC as used in clinical practice. We believe that the presentation of the study in the abstract is fair and fully justified by the data.

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.

Response (page 3):
We have modified the background section in accord with the request of the reviewer.

3) Methods:
(a) Were patients requiring hemodialysis or hemofiltration excluded?

Response (page 12):
We have modified the manuscript to make it clear that those on RRT were 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.

Response (page 8):
We have modified the discussion to indicate that the decreases in renal function that we reported in Table 3 are consistent with mild to moderate levels of RIFLE classification of renal dysfunction.

4) Results
(a) Nephrotoxic agents: these should be presented in detail, for all groups, and if possible duration of administration

Response (page 5 and Table 1):
The space available to report the 1940 medications in the 128 patients, or an average of 15 medications per patient precludes our complying with this request. We have provided a list of the classes of these medications and detailed the number of patients in each antifungal treatment group that was on 1 or more than one nephrotoxin. DRL evaluated each of these medications and classified each as a potential nephrotoxin or not in a blinded fashion. There was no significant difference in the distribution of nephrotoxins per treatment group except that 74% of the voriconazole (test) group was overweighted compared with the other two treatment groups.

(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?

Response (Table 1):
We have included the mean, median, and range of treatment duration in Table 1 in the revised manuscript.

(c) Voriconazole levels: were they drawn in any of these patients? What doses of voriconazole were administered? Loading doses were given to all patients?

Response (page 9 – 10):
A second paragraph of limitations has been added to the Discussion of the revised manuscript. Dosing was monitored by a clinical pharmacist and was in strict accord with the manufacturer’s recommendations as detailed in the FDA-approved package insert. Drug levels were not measured as TDM of voriconazole was not established as a standard of care nor is it adopted in most institutions at this time (although we think TDM would be a clinical method to monitor exposure of voriconazole).

(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)?

Response (page 9 and Table 1):
Underlying conditions were collected and added to Table 1.
(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.

Response (Table 1):
Cases classified as confirmed by culture were included only when the clinical service Infection Diseases Consultant believed that infection was present. We have added a footnote to Table 1 to address this issue.

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

Response (Table 1):
We have added a differentiation between prophylaxis, empiric, and presumed/confirmed as defined by the EORTC guidelines (2008 CID) in Table 1.

(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.

Response (page 13):
We have modified the manuscript to indicate that the independent variables entered in to the model were prespecified and the prespecified p value used for their retention. We have also modified the results section on page 8 to more clearly present which of these variables met the inclusion criteria and our prespecified criteria for being identified as statistically significant.

5) Discussion
(a) The second paragraph is not adding much to the Discussion.

Response:
We appreciate the Reviewer’s point of view and those of the other Reviewers. In balance, we consider this paragraph important in that it places the development of voriconazole in context. It was a tribute to
the chemists and biologists at Pfizer that they persevered countless efforts to improve on the SAR of fluconazole and then ~1500 salts to be able to develop an intravenous formulation of voriconazole. We agree with Reviewer #3 who states: “Pages 7 and 8 are of great importance and benefits from the “behind the scenes” look at the development of voriconazole...”. We believe that the Readers of the Journal will also benefit from the behind the scenes development efforts of not only an antifungal but the molecular modeling approach to drug development. Voriconazole represented one of the first successes in molecular modeling in the industry.

(b) More recent data on the use of IV VOR in patients with renal dysfunction should be referenced in Discussion paragraph 4.

Response (page 8 and References):
We completely agree and have amended the paper accordingly. The data by Neofytos et al (Reviewer #2) and Oude Lashof (really Kullberg) et al are important additions to our paper which appeared in publication after we submitted our manuscript for review. These have been added to the References and cited in the Discussion section. Specifically, the scholarly paper by Neofytos mirrors the conclusions of our paper and represents real-world experience as opposed to a re-evaluation of the Candidemia database from the Phase 3 study, which on its own are important data as well.

(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? ).

Response (pages 9 & 11):
The size and nature of our study do not allow conclusions regarding this point. Clinical studies are expected to raise new questions and we have modified the discussion section to indicate that this association should be the subject of future investigation. Indeed others have also noted that invasive candidiasis has shown increased mortality compared with those infected with Aspergillus (Neofytos CID 2009).

(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?

Response (page 9):
We have modified the manuscript to indicate that it has been our experience that clinicians reach for voriconazole when mould is suspected or for prophylaxis in the setting of acute myelogenous leukemia. That the patients treated with voriconazole had less renal compromise could also reflect the precaution in the voriconazole label regarding Clcr < 50 mL/min. Despite having some renal compromise, clinicians used voriconazole due to the underlying pathogen or risk of infection.

6) Figure 1: not needed
Response:
Figure 1 has been deleted.

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.
Response:
All patients had chronic renal insufficiency. What we studied was the onset of acute kidney injury.

8) Table 4: not needed.
Response (page 6):
We agree that the data from Table 4 appear in the text, and have removed Table 4 from the manuscript.
Reviewer #3 comments

In patient matching by comorbidity what criteria were used? Charlson’s scoring? I do not see this information in the manuscript and see only DM and cardiovascular disease.

Response (Table 1):

We did not attempt to match the subjects, rather we measured the comorbidities in the groups and performed additional analyses that could adjust for differences among the groups.

Were patient median or nadir blood pressure results available? This may be an easy variable that helps to explain the nephrotoxicity behind candidemia treatment vs. the vori treated group which was primarily aspergillosis.

Response:

We did not collect blood pressure in this study but have included admission to an ICU as a surrogate for physiological instability.

I am unable to determine if contrasted imaging studies were more commonly obtained in one particular group over another. Intuitively those with candida more likely have intraabdominal infections than those with aspergillosis and may have received more contrasted imaging studies as a result confounding the variables evaluated. Please clarify if this was evaluated.

Response:

Nephrotoxic contrast was so rarely given in this population with a strong contraindication that we did not include its measurement as part of the study.

Pages 7 and 8 are of great importance and this paper undoubtedly benefits from the “behind the scenes” look at the development of voriconazole the authors are able to provide given past affiliations with Pfizer and likely long experience with the development of IV vori, however it reads promotional in some ways. The sentence preceding reference 12 on page 7 should be altered to say something close to, “However at the time of FDA approval....” etc.

Response (page 7):

Thank you for this comment on the history of the development of voriconazole. We have modified this section.
P values should be included in the results portion of the text where appropriate. When comparing three
groups it is not typical to list a P value for “overall difference”. The authors should consider further
expanding their explanation of this in the text instead.

Response:
We have modified the tables to identify the comparisons for which the p values were calculated where
this is not evident from visualization of the primary data.

Others have recently performed similar studies and these results should be included in the authors
discussion and referenced: Oude Lashof AM, et al. Safety and tolerability of voriconazole in patients with

Response (page 8):
The Oude Lashof paper was published after submitting our manuscript for review. It is important to
note that the data from the Oude Lashof paper had been presented at ICAAC 2010 and cited in our
original manuscript (Ref #10). We have added the Oude Lashof and the Neofytos (CID 2012) papers to
the revised manuscript.