Author's response to reviews

Title: Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematological patients

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Author's response to reviews: see over
DEAR EDITOR,

please find enclosed the revised version of the above-mentioned manuscript.
I would like to thank you and the reviewers for the useful comments and suggestions aiming at improving the manuscript. Our replay to the points raised by the reviewers are as follows:

Reviewer 1 (JR Wingard)

1 Query (1Q): This observational study does not allow to ascertain if the combination is any better than the monotherapy without caspofungin. This should be explicitly stated in the discussion.

1 Replay (1R): we agree and the following sentence has been added to the discussion section (page 12) “However, the retrospective design of this study did not allow to ascertain clearly if the combination caspofungin-based combination therapy was significantly better than any other monotherapy without caspofungin”.

2 and 3 Q: page 8. How many received itraconazole? Were they given a polyene or voriconazole and what was the response? How many received a lipid amphotericin empirically before diagnosis, and at what dose, and what were they given for treatment (polyene or voriconazole)?

2R: the number of patients who received itraconazole (only 1) before combination therapy has been specified in the text (see pag.8). This patient was started on combination of liposomal amphotericin B and caspofungin thereafter. No patient received lipid amphotericin B before combination therapy because liposomal amphotericin B was the preferred formulation among Italian pediatric centers. The dose of liposomal amphotericin B used in the study is given at page 9.

4Q: State the criteria used for failure and after how many days. Clinical symptoms often are slow to respond and radiography typically worsens during the first 7-10 days and these criteria cannot be reliably used to declare failure. These points need to be addressed in the discussion.

4R: This study adopted a standard criterium to define the failure of the previous antifungal therapy, i.e. the failure to improve clinically and radiographically despite ≥ 7 days of standard therapy. This criterium has been adopted for other retrospective and prospective studies on combination therapy; for instance, see Aliff TB et al. Cancer 2003; Kontoyiannis DP et al. Cancer 2003; Marr KA et al. Clin Infect Dis 2004; Maertens et al Cancer 2006.
Considering that this is a retrospective study, we could not define “a priori” the time for switching to combination therapy. Anyway, if one look at the median time of starting combination therapy in patients who were already on antifungal therapy, one can see that this was 13 days for patients already on prophylaxis with fluconazole or itraconazole; 10 days for patients already on empiric antifungal monotherapy; and 8 days for patients already on fist-line antifungal monotherapy, respectively. This is clearly stated in the text (see pag 8). The limitations of this study due to its retrospective design has been added to discussion (see replay 1)

5Q: The fact that there was no difference in early or late start of caspofungin as to response rate suggests that the addition of caspofungin did not play a role in whether or not the pt responded.

5R: actually, we found and commented the fact that the adoption of a caspofungin-based combination therapy (not the simple adding of caspofungin) within or after 7 days from diagnosis of IA did not seem to play a role in determining a favourable outcome. In another words, in a group of 40 patients who received a combination therapy for a median of 29 days after diagnosis of IA, the starting of combination therapy within or after 7 days from diagnosis of IA did not impact on the response rate and outcome. Perhaps, this may reflect what the reviewer expressed at the point 4Q.

Reviewer 2 (WJ Steinbach)

1Q: another relevant reference is the Maertens reference in Cancer that outlined a similar study in adult patients

1R: The paper by Maertens et al Cancer 2006 was already comprised in the reference list as reference 40 and commented with a sentence in the discussion section (see page 12)

2Q: The details of the patients in page 7-8 could be best summarized in a table and therefore not repeated in the text

2R: The main demographic and clinical characteristics of the patients are showed in table 1. The text in the results section has been shortened accordingly.

3Q: the tables show group A and B, but what we need to see is primary vs. salvage therapy as well mentioned in the text, how did those results differ (most are salvage therapy)

3R: we added to Materials and Methods (definition paragraph) the definition of primary and salvage therapy “For the purposes of this study, the caspofungin-based combination therapy was considered as primary therapy if the patients were not receiving any mould-active antifungal drug or were on prophylaxis with fluconazole or itraconazole; and as salvage therapy if the patients were receiving empirically or therapeutically any mould-active antifungal monotherapy, at diagnosis of IA, respectively” (see page 5). Moreover, the variable (caspofungin-based combination therapy given as primary or salvage treatment) has been added to the analysis of prognostic factors predictive of outcome (see table 3).

4Q: page 8-it is still not completely clear, all but 7 patients were on salvage combination therapy?
4R: see replay to point 3Q

4Q: the dose of voriconazole is low for children?

5R: the dose of voriconazole used in this study is that reported in the market instruction by the company. Only recently, the recommended dose for children 2-12 year-old have been changed by the company.

6Q: How was the “timing of adoption of combination therapy” defined-timing from what point? 7 days after diagnosis

6R: This study adopted a standard criterium to define the failure of the previous antifungal therapy, i.e. the failure to improve clinically and radiographically despite ≥ 7 days of standard therapy. This criterium has been adopted for other retrospective and prospective studies on combination therapy; for instance, see Aliff TB et al. Cancer 2003; Kontoyiannis DP et al. Cancer 2003; Marr KA et al. Clin Infect Dis 2004; Maertens et al Cancer 2006.
Considering that this is a retrospective study, we could not define “a priori” the time for switching to combination therapy. Anyway, if one look at the median time of starting combination therapy in patients who were already on antifungal therapy, one can see that this was 13 days for patients already on prophylaxis with fluconazole or itraconazole; 10 days for patients already on empiric antifungal monotherapy; and 8 days for patients already on fist-line antifungal monotherapy, respectively. This is clearly stated in the text (see pag 8).

7Q: Figure 1b and 1 c should be “days” not “years” in the X axis label

7R: we corrected figure 1 b, that refers to Kaplan-Meier estimate of 100-day survival; whilst figure 1c, that refers to OS (median follow-up 0.7 years, range 100 days-3.1 yrs), years in X axis label is correct.

8Q: so, underlying disease was the best predictor of outcome?
8R: our data suggest that the status of underlying disease is very important in predicting the response to antifungal therapy.

We think to have adequately addressed to all the queries raised by reviewers and that the paper is now worth publishing in BMC Infectious Diseases.
I look forward to hearing from you at your earliest convenience.

Yours sincerely,

On behalf of all authors

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