Author's response to reviews

Title: Analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation

Authors:

Michaela Doering (Michaela.Doering@med.uni-tuebingen.de)
Carsten Mueller (c.mueller@uni-koeln.de)
Pascal-David Johann (pascal.johann@med.uni-heidelberg.de)
Annika Erbacher (Annika.Erbacher@med.uni-tuebingen.de)
Astrid Kimmig (Astrid.Kimmig@med.uni-tuebingen.de)
Carl-Philipp Schwarze (Carl-Philipp.Schwarze@med.uni-tuebingen.de)
Peter Lang (Peter.Lang@med.uni-tuebingen.de)
Rupert Handgretinger (Rupert.Handgretinger@med.uni-tuebingen.de)
Ingo Mueller (i.mueller@uke.de)

Version: 3 Date: 16 August 2012

Author's response to reviews: see over
Re: Revised manuscript submission MS ID: 1011884671661746

Dear Dr Marshall,

Thank you for giving us the opportunity to revise our abovementioned manuscript on the analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation. Please find our point-by-point replies to the reviewers comments attached. In addition, we provide a copy of the local IRB decision and the revised manuscript. We hope that the manuscript in its improved version is now acceptable for publication in *BMC Infectious Disease*. We would be happy to provide any additional information you may require.

Sincerely,

Dr. Michaela Döring
Major compulsory revisions

1. Posaconazole is currently unlicensed for use in children and the age of 12 years. The authors should clearly state this fact. Furthermore, there is currently no reliable pharmacokinetic data on posaconazole in children. Simple extrapolation from adult pharmacokinetics is generally not sufficiently accurate. Why did the authors choose posaconazole over antifungals that have been studied in this age group? As this is a retrospective review, were these 60 patients given posaconazole because they were intolerant to other antifungals?

There was no drug licensed in Germany for antifungal prophylaxis in children after BMT at the time of this retrospective survey. We observed breakthrough infections under other azoles. Therefore, we choose posaconazole after the promising results from adult patients. We were aware of the pharmacokinetic problem, this is why we conducted plasma level measurements.

2. Page 12, paragraph 1: If patients were readmitted for reasons other than IFI and received IV antifungals they were excluded from the analysis. This decision may bias the analysis because readmission could be related to posaconazole adverse effects, and therefore intolerance may be underappreciated. How many patients started on posaconazole were excluded based on this criterion? Are these the 4 patients mentioned on pages 5 and 6?

On page 9 the following paragraph was added: “Because of post-transplant complications in two patients with intestinal graft-versus-host disease and two patients with severe bacterial infection, oral posaconazole was replaced by intravenous caspofungin. These patients were included in the analysis up to the moment of change of the antifungal prophylaxis.”

3. Unlike adult patients in the Ullman study, only ~10% of the patients in this study had GVH grade 3 or 4 (Table 1). This may be related to the difficulty in ensuring oral intake in these patients. Moreover, none of the patients that underwent therapeutic drug level monitoring had GVH 3 or 4 (Table 3). Thus TDM results may represent an overestimation for patients with GVH which currently represent the main target population for posaconazole prophylaxis in SCT recipients.

Pediatric patients with grade 3 or 4 GvHD are not at all the main target population. These patients are typically hospitalized and require iv TPN and fluids. To ensure antifungal prophylaxis these patients receive intravenous antifungal prophylaxis.

4. Although there were no cases of probable-proven IFI, the background risk of IFI may have been low given that most patients did not have significant GVH. Some appreciation of the efficacy of posaconazole may be gained from historical severity-matched controls which would address the
background risk of IFI in this patient population.

GvHD is less frequent in children than in adults. On the other side, more patients receive a T-cell depleted graft. It is difficult to compare these two risks. As there is no standard medication for oral antifungal prophylaxis after allogeneic BMT, and all patients receive “some” prophylaxis, the comparator would be very vague. We agree, that this issue definitely needs to be addressed in a prospective trial.

5. Posaconazole exposure of >700 ng/mL has been shown to correlate with efficacy during prophylactic treatment (Dolton et al. AAC 2012). Thus, most of the patients in this study had low, possibly subtherapeutic posaconazole levels in plasma. The authors discuss some of the reasons for this fact (poor oral intake, concomitant PPI use). This issue should underscore the need for dose finding studies of posaconazole in children aged <12 years.

We agree completely and these studies are underway to our knowledge already.

6. Patients were treated from discharge to day 100 post transplant, and then until T cell function recovery. However the actual duration (median and range) of posaconazole treatment is not clearly stated.

On page 9 the following sentence was added: “The application period for posaconazole was 127 days (range 12 - 188 days).”

7. The observation period was from the start of posa treatment and until day 200 post SCT. However, the range of observation period was from 12 to 188 days (median 162 days), and 35% of patients were not monitored until day 200. As there were no cases of probable-proven IFI, were these patients taken off of posa because of adverse effects, or because of possible IFI?

As the reviewer pointed out under number 6, the treatment period was at least until day +100. The observation period, however, was intended to exceed this period in order to pick up potential breakthrough infections, which were diagnosed early after the end of posaconazole and may have originated already under prophylaxis. As there was no case like this in the end, one could also omit this information, we think it is more appropriate to give this information.

Minor essential revisions

8. Page 8. Rantidine is an H2 receptor blocker, not a proton pump inhibitor.

Changed

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:

I have served on an advisory board for Pfizer.
Reviewer’s report

Title: Safety and efficacy analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation

Version: 2 Date: 12 June 2012

Reviewer: Andrea Page

Reviewer’s report:

The authors have conducted a retrospective review of their single-centre experience with the use of posaconazole prophylaxis following hospital discharge for allogeneic stem cell transplantation in children under the age of 11 years. With 60 patients included in the review, it is the largest study to date on the use of posaconazole in the paediatric population whether for treatment or prophylaxis, and as such, adds significantly to the literature. Nonetheless, a number of additions and clarifications would further strengthen the report and should be addressed before publication.

Major Compulsory Revisions:

1. Further clarification is needed in terms of the selection of patients. Was this group 60 consecutive patients, patients who received posaconazole based on physician preference, or a convenience sample selected from amongst all those who received posaconazole? If the latter, how were the included patients selected?

The group consisted of 60 consecutive patients during the observation period.

2. For other physicians to apply this data to their own clinical practice, more detail is needed in the methods section (or in Tables 1 and 3) regarding policies and practices at your institution. For instance, what conditioning regimens were used?

On page 8, the following paragraph was added: „30 of the 60 pediatric patients received a myeloablative conditioning regimen (MAC), from which 12 of 30 received TBI, 2 of 30 were treated with busulfan, and 16 of 30 with treosulfan. 20 of the 60 pediatric patients received a reduced-intensity conditioning regimen (RIC) with melphalan. 5 patients received a conditioning regimen with fludarabin and thiotepa, 4 patients with fludarabin and cyclophosphamide, and 1 patient with thiotepa and cyclophosphamide. Patients receiving a graft from a MUD, MMUD or MFD received short course MTX and CsA. Patients undergoing haploidentical transplantation received a T-cell depleted graft and mycophenolate mofetil only."

3. What other prophylactic antimicrobials were given?

Children received cotrimoxazole and acyclovir simultaneously with posaconazole.

4. Why were liposomal amphotericin B and caspofungin used during the inpatient period and what governed the choice between the two?

On page 4, the following paragraph was added: “In our clinic, the intravenous antifungal prophylaxis in pediatric HSCT recipients consisted of liposomal amphotericin B (1 mg/kg/day) during conditioning.
On day +1 after HSCT we changed to caspofungin in a dosage of 1 x 50 mg/m²/day due to lower nephrotoxicity with comparable efficacy.” For details please refer to our recently published manuscript by Döring et al., BMC Infect Dis. 2012; 12:151.

5. What was the mean/median duration of neutropenia pre-engraftment?

On page 9, the following paragraph was added: “The median duration of neutropenia pre-engraftment was 12 days (range 10 – 24 days), mean 12.58 ± 1.84.”

6. How long did patients remain hospitalized, and conversely, on what day post-transplant was posaconazole initiated?

Posaconazole was only given in the outpatient setting and initiated two to four days before discharge, which was three weeks after HSCT in most cases.

7. What methods were used to prevent GVHD and how many patients required treatment?

Patients receiving a graft from a MUD, MMUD or MFD received short course MTX and CsA. Patients undergoing haploidentical transplantation received a T-cell depleted graft and mycophenolate mofetil only. All Patients with GvHD listed in Table 1 were treated.

8. Amongst patients who had posaconazole levels measured, how many had diarrhea (a potential cause of low trough levels)?

On page 12, the following sentence was added: “Three of 24 pediatric patients in whom posaconazole trough levels were measured experienced diarrhea.”

9. Although no fungal infections were seen during this study, it would be helpful to know how many infections were expected. Is there a historical or contemporary control group that received a different antifungal prophylaxis regimen, and if so, what is the rate of invasive fungal infections in this group? Failing that, some mention should be made of the anticipated rate of fungal infections based on other published studies.

On page 13, the following passage was added: “In a historical group of 50 pediatric patients whom we had treated in our center with an antifungal prophylaxis with itraconazole after allogeneic HSCT, three possible fungal infections were observed. This data is in concordance with data obtained at other centers (Grigull L et al., 2007).”

10. There is a great deal of controversy in the literature about the use of therapeutic drug monitoring of posaconazole in both the adult and paediatric populations. Since the authors have measured posaconazole trough levels and devote significant space in the results section to the presentation of these levels, the controversy should be more clearly addressed in the discussion. For instance, there is some (but not universally corroborated) data to suggest that clinical outcomes in treatment and prophylaxis correlate with levels of >0.5 mg/L (or even 0.7 mg/L), causing some authors to advocate targeting these levels. (0.5 mg/L is also the MIC90 for most fungi targeted by posaconazole). These levels were not, in general, achieved in this study, yet no fungal infections were documented. This potential discrepancy should be directly addressed. The authors also state, in paragraph 1 of the Discussion, that “posaconazole trough concentrations ... were ... comparable with those of adults during posaconazole prophylaxis”. In both of the studies referenced (11, 12), the mean concentrations were higher in the adult patients (significantly so in the paper by Ullmann et al and less so in that by Cornely et al).
A paragraph was added on page 14. “Posaconazole trough levels were more stable and only slightly lower than…”

11. The authors included posaconazole Ctrough measurements from day 3-6 in the overall mean and median calculations, however, since steady state is not reached until day 7, perhaps only measurements on day 7 or after should be included in the overall analysis of posaconazole levels. Likewise, the authors make numerous statements throughout the manuscript regarding the stability of posaconazole levels over time, but we are provided with no statistical or graphical evidence of this. With multiple Ctrough levels measured repeatedly in individual patients over a prolonged period of time, the authors have a unique data set that should be presented more fully.

The term „stability“ refers to the frequency of higher levels, not to multiple measurements in the same patient. Accessible data is presented and further analyses require a standardized sampling within a prospective trial.

**Minor Essential Revisions:**

1. I would suggest consistent use of the term "antifungal" throughout, rather than "antimycotic"
   Done

2. Zygomycetes is no longer the preferred term. The third sentence in the background section should be adjusted to state that posaconazole has activity against "Candida spp., Aspergillus spp., Cryptococcus spp., and certain agents of mucormycosis and fusariosis".
   Done

3. Background, last sentence of the first paragraph: "comparably" should be removed, as reference 13 was a retrospective review without historical or contemporary comparator group reported.
   Done

4. Background, first sentence of the second paragraph: "as well as the absence of pediatric studies with high patient numbers" should be removed, as this is a rationale for reporting clinical experience, not for making the decision to use posaconazole.
   Done

5. Patient characteristics -Please specify whether or not any other changes to the allogeneic hematopoietic stem cell (HSCT) protocol or prophylaxis were made coincident with the change in posaconazole dosing.
   Done

6. Patient characteristics -The duration of the observation period varied widely (12 to 188 days). Please specify how many patients were monitored for < 100 days post-HSCT.
   Done, p. 9

7. Efficacy analysis -Please define "transplant-related multiple organ failure" as the cause of death for some of the patients. Does this mean bone marrow failure? Could it have been related to an occult or unrecognized invasive fungal infection?
Autopsies were not performed; therefore no further specification can be made.

8. Safety and tolerability analysis - Please replace "itching" with "pruritus". The change should be made throughout. Please add the word "severity" to the end of the second sentence.

Done

9. Safety and tolerability analysis - Did any of the adverse events require cessation of therapy?

Added on p.10.

10. Cyclosporin A levels - Did any patients require a second adjustment of their cyclosporin doses when levels were next measured at days 8-12 or 16-20? This is particularly important since posaconazole levels would not have reached steady state at the time of first dose adjustment.

One of twelve patient required further dose adjustment

11. Posaconazole levels, next-to-last sentence - "Patients who received posaconazole tid showed LOWER trough levels between days 3 and 6 than those after day 7"

Changed

12. Posaconazole levels, last sentence - Ranitidine is an H2-antagonist, not a proton pump inhibitor. Provide either the percentage of patients receiving a true proton pump inhibitor (preferred) or change the phrase to "gastric acid suppressing agents". This should also be addressed in the discussion.

Done

13. Discussion - It is not clear what is meant by "partially invasive fungal infections" and the term should be adjusted. In addition, this study included 15 patients, of whom 12 had proven or probable invasive aspergillosis, 3 were prescribed posaconazole for prophylaxis, and only 9 were post-HSCT. This should also be clarified.

Done

14. Discussion, 3rd last sentence - add "inhibitors" after calcineurin.

Done

15. Abbreviations and Table 2 - Cyclosporin is spelt incorrectly.

Corrected

16. Table 1, 2, and 3 - Each use of Grade of GVHD needs an "e", and similarly alanine and aspartate in Table 2.

Corrected

Level of interest: An article whose findings are important to those with closely related research interests Quality of written English: Acceptable Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.