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?

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?
   What other prophylactic antimicrobials were given?
   Why were liposomal amphotericin B and caspofungin used during the inpatient period and what governed the choice between the two?
   What was the mean/median duration of neutropenia pre-engraftment?
   How long did patients remain hospitalized, and conversely, on what day post-transplant was posaconazole initiated?
   What methods were used to prevent GVHD and how many patients required treatment?
   Amongst patients who had posaconazole levels measured, how many had diarrhea (a potential cause of low Ctrough levels)?

3. 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.

4. 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).

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.

Minor Essential Revisions:

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

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".

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.

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.

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.

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.

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?

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.

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

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.

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"

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.

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.

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

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

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

**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.