Author's response to reviews

Title: Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients

Authors:

Eric J Bow (EJBow001@shaw.ca)
David J Vanness (dvanness@wisc.edu)
Monica Slavin (Monica.Slavin@mh.org.au)
Catherine Cordonnier (carlcord@club-internet.fr)
Oliver A Cornely (oliver.cornely@zks-koeln.de)
David I Marks (David.Marks@UHBristol.nhs.uk)
Antonio Pagliuca (antonio.pagliuca@kcl.ac.uk)
Carlos Solano (solano_car@gva.es)
Lael Cragin (lael.cragin@unitedbiosource.com)
Alissa J Shaul (Alissa.Shaul@evidera.com)
Sonja Sorensen (Sonja.Sorensen@evidera.com)
Richard Chambers (Richard.Chambers@pfizer.com)
Michal Kantecki (Michal.Kantecki@Pfizer.com)
David Weinstein (David.Weinstein@pfizer.com)
Haran Schlamm (HTSchlamm@att.net)

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Author's response to reviews: see over
Philippa Harris
Executive Editor
BMC Infectious Diseases
BioMed Central
236 Gray’s Inn Road
London WC1X 8HB
United Kingdom

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Dear Philippa,

Re: Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients

On behalf of my co-authors, and further to our previous submission (MS: 1458051408125318), I would like to submit the above-entitled work for consideration for publication in BMC Infectious Diseases. Please find our responses to the reviewer comments below.
I can confirm that all authors have seen and approved the revised draft manuscript, and that they have contributed significantly to the work. The manuscript has not been previously published and is not under consideration for publication by any other journal.

Thank you for considering this original work for peer review and potential publication in the *BMC Infectious Diseases*.

We look forward to your response.

Yours sincerely,

E.J. Bow, MD, MSc., D. Bacteriol., FRCPC
Infectious Diseases, Haematology/Oncology, Blood & Marrow Transplant
Professor, Departments of Medical Microbiology & Internal Medicine,
University of Manitoba;
Medical Director, Clinical and Academic Services, and Infection Control Services,
CancerCare Manitoba.

675 McDermot Ave.
Winnipeg, MB, Canada R3E 0V9
Tel: 204-787-3964
Fax: 204-786-0196
e-mail: Eric.Bow@cancercare.mb.ca
Reviewer #1 Report (John R Wingard)

Comments:
1.1: Minor: In your discussion, please discuss the limitations of lumping together studies that had different dose schedules, different start dates (Ullmann study only in GVHD), different risk groups, different transplant conditioning regimens, imbalances that affect IFD risk (Winston study), problems with toxicity resulting in stopping the trial (Marr trial), different dose schedules and compliance differences.

Response: In response to the reviewer’s suggestions, we have provided some further discussion at the beginning of page 14, paragraph 3, to describe the impact on the analysis of the inclusion of these heterogeneous studies.

Reviewer #2 Report (Peg Carver)

Comments:
2.1: This manuscript provides a meta-analysis of antifungal prophylaxis in allogeneic hematopoietic cell transplant recipients. I will note that I am not an expert in meta-analyses and thus cannot comment on the methodology utilized for that analysis. While an interesting analysis, the authors included very few studies as the basis for their analysis. The rationale for inclusion or exclusion of studies was poorly defined (with the exception of the explanation provided for the Slavin study), and further clarification is required prior to recommending publication of this manuscript.

Although a discussion of the results of a 2007 meta-analysis was included, a (more) recent meta-analysis by Ziakis et al[1] was not presented. Comparison of the Ziakis and Robenshtok studies’ methodology and results to that of the current analysis would be beneficial.

Response: Both the recently published meta-analysis by Ziakas and colleagues [1] and the earlier study by Robenshtok and colleagues [2] investigated the comparative effectiveness of systemic antifungal prophylaxis through a combination of direct comparison using the classical random-effects method of DerSimonian and Laird [3] (if there were sufficient studies comparing the same treatment) and indirect comparison using either, in the case of Ziakas and colleagues, the classical random-effects method of Lumley [4] or, in the case of Robenshtok and colleagues, the simple adjusted indirect comparison approach of Bucher...
and colleagues [5]. Our study, in contrast, simultaneously incorporated both direct and indirect evidence into a single mixed-treatment comparison model following the method outlined by Lu and Ades [6], which allows indirect evidence to both supplement and substitute for head-to-head comparison. Furthermore, our approach used Bayesian estimation methods, which provide interpretable ranges of uncertainty based on actual sample size rather than asymptotic approximations, and allow direct statements about the probability that each treatment surpasses the others in effectiveness.

Please note, we have included some additional text in the Introduction page 4, paragraph 1 highlighting the study by Ziakis et al:

“Although a meta-analysis published in 2007 concluded that antifungal prophylaxis reduced all-cause mortality, IFI-related mortality, and IFI incidence in alloHCT recipients [8], a more recent systematic review failed to demonstrate consistent treatment effects for these outcomes using direct and indirect comparisons.”


2.2: Similar to the Robenshtok analysis, these authors concluded that there was comparable effectiveness of antifungal drugs, while acknowledging the paucity of comparable studies for newer, possibly more effective agents such as micafungin, voriconazole, and posaconazole.
I disagree with excluding the Slavin fluconazole vs placebo study [26]. The fact that neither arm had mold coverage is important in evaluating the overall efficacy (or lack thereof) of various antifungal regimens. While the reference is ‘old’, and would likely underestimate the incidence of mold infections, it would still be of value to include while noting that caveat. How was ‘old’ defined/determined?

Response: We can confirm that the Slavin et al. (1995) study only contributed evidence for a comparison that was not of interest (fluconazole versus placebo); thus, its inclusion in the evidence network was considered largely extraneous and was expected to contribute only minor effects on the estimated odds-ratios of interest. To confirm this, we conducted a test analysis adding data from the Slavin et al. (1995) study on proven/probable invasive fungal infection (fluconazole: 10/152 and placebo: 26/148), which demonstrates that the effect on results was trivial (please see comparison of results in the table below – bold for original analysis, italic for analysis including Slavin et al. (1995)). We have revised the manuscript to acknowledge those RCTs that met our search criteria but that were not included in the final MTC analysis (due to lack of a common comparator) – please see “Methods – Systematic literature review” on page 6 for clarification.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Median posterior odds-ratio relative to fluconazole (interquartile range)</th>
<th>Posterior probability of having lower incidence than fluconazole</th>
<th>Posterior probability of having the lowest incidence of all treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven/probable IFI at 180 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>–</td>
<td>–</td>
<td>2%</td>
</tr>
<tr>
<td>(Including Slavin)</td>
<td>0.52 (0.35–0.76)</td>
<td>84%</td>
<td>2%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.52 (0.35-0.77)</td>
<td>85%</td>
<td>25%</td>
</tr>
<tr>
<td>(Including Slavin)</td>
<td>0.56 (0.32–0.99)</td>
<td>75%</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>0.56 (0.33–0.98)</td>
<td>76%</td>
<td>31%</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>0.46 (0.28–0.73)</td>
<td>84%</td>
<td>39%</td>
</tr>
<tr>
<td>(Including Slavin)</td>
<td>0.46 (0.28–0.73)</td>
<td>85%</td>
<td>39%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.3: The authors appear to have confined their analysis to trials which included ONLY alloHSCT patients, and thus, excluded a number of trials [2-13] including the excluded Slavin study [3] which included both allo and auto transplant patients (several of these references [2, 3, 7, 8] are ‘older’ studies if 1995 is the ‘cutoff’ for being too old]. I recognize that patient level data may not be readily available from these trials; however, excluding them is an important difference in this study vs previous meta-analyses, and the decision defending this should be discussed. It should be noted, however, that a newer (2012) study by Chaftari et al which compared posaconazole and weekly ABLC that included only alloHSCT which was not included (or mentioned) [14]. The relative ‘risk’ of HSCT patients differs greatly if they have GVHD; however, many studies do not include this level of detail in their publications, making comparisons between studies difficult.

Response: We assumed, based upon previously published systematic reviews with meta-analyses, that anti-fungal prophylaxis was efficacious. The intent of our study was to provide a framework for choosing a prophylactic antifungal agent for use in stem cell transplant recipients from among the availableazole anti-fungal agents using mixed treatment comparisons i.e., a network meta-analysis procedure whereby head-to-head treatment comparisons can be made, provided that the treatment comparisons share one or more common comparators in a network of evidence. For this we restricted our analyses to randomised-controlled trials that contained the azole anti-fungal agents of interest. Studies examining non-azole comparators (such as the placebo-based study of Slavin and colleagues [1995, reference #34] or the study by Chaftari et al. [2012, reference #30] comparing posaconazole and intravenous ABLC) could not inform our conclusions; accordingly, such studies were excluded. We have added some further explanation of this approach under the “Methods – Systematic literature review” on page 6 for clarification:

“Only RCTs meeting the search criteria were included in the MTC network analysis of fluconazole, itraconazole, posaconazole, and voriconazole if they included a comparator common to multiple RCTs. For example, the hypothetical common comparator “C” can indirectly link comparators of interest “A” and “B” in Trial 1 comparing interventions “A” versus “C” and Trial 2 comparing “B” versus “C”. However, Trial 3 comparing “B” versus “D” would not be included in the hypothetical “A” vs “B” network since comparator “D” is neither
a comparator of interest nor a common comparator that can indirectly inform an “A” vs “B” comparison.”

Reviewer #3 Report (Panayiotis Ziakas)

Comments:
3.1: General: The authors used a Bayesian approach to quantify the effects of randomized trials in oral antifungal prophylaxis in HSCT. The outcomes of interest were IFIs and mortality

Response: General comment, none required.

3.2: Major: Comparisons derive from a small number of pertinent studies and indirect comparisons predominate. The constituting studies allow for the use of intravenous formulation of fluconazole and itraconazole, consequently the exclusion of studies that use (obligatory) intravenous drugs for prophylaxis (e.g. amphotericin, micafungin) may be not justified.

Response: The included studies did permit the use of parenteral formulations to account for periods of reduced oral tolerance attributable to oral mucositis or graft-versus-host disease. As suggested below (3.3), the effects of prophylaxis were a function of an “average exposure” that was predominantly a function of the oral formulations. We chose not to examine strategies that were solely a function of parenterally administered anti-fungal formulations.

3.3: Additionally, the relative effects do not represent the effects of oral administration but the “average” pharmacologic effects without adjusting for route of administration. The setting of meta-analysis does not generally allow for adjustment of effects by route, duration, or dose of administered drugs.

Response: Thank you for this observation. Whilst we agree with this point, we were unable to identify a method to adjust for this bias.

3.4: Between-study clinical heterogeneity is a concern, particularly regarding the inclusion of posaconazole trial in that setting. Posaconazole is effective in neutropenia after chemo or MDS over flu/itra (Cornely OA, et al. N Engl J Med. 2007;356:348-59) but in HSCT it was
tested only in the context of severe GvHD II-IV (no data on early neutropenic phase as acknowledged by ECIL in Maertens J, et al. Bone Marrow Transplant. 2011;46:709-18).

Response: The study by Ullmann and colleagues (2007) represented the only examination of the clinical effect of posaconazole prophylaxis in HSCT recipients. It is acknowledged that there were differences in study drug start dates among the included trials. The discussion has been modified to this effect on page 15 of the revised manuscript. The decision to include this trial is validated by the alignment of the results of the base-case analysis with that of the post-hoc sensitivity analysis in which the study was excluded.

3.5: In strict terms, perhaps this study should not be included in the matrix of comparisons. Outcomes were defined based on EORT/MSG, 2002. They were revisedUPDATED IN 2008.

Response: The classification of IFIs in each of the studies was based upon the definitions used by the authors of the included studies. All (Winston et al., Marr et al., Ullmann et al., Marks et al., and Wingard et al.) were based upon the 2002 definitions.

3.6: The potential impact of adopted changes (regarding the outcome definitions) should be discussed at least as a limitation section (De Pauw B, et al. Clin Infect Dis. 2008;46:1813-21). The findings were not discussed in the context of similar analyses, where a frequentist approach was used (e.g. Ziakas PD, et al. Clin Ther. 2014;36:292-306).

Response: Use of the 2008 IFD definitions for outcome identification may well have added robustness to the outcomes detected. A recent study using these revised definitions for assessing the outcome of treatment for IA seemed to have that effect (Herbrecht R, Patterson TF, Slavin MA, et al. Application of the 2008 Definitions for Invasive Fungal Diseases to the Trial Comparing Voriconazole versus Amphotericin B for Therapy of Invasive Aspergillosis. A Collaborative Study of the Mycoses Study Group (MSG 05) and the EORTC Infectious Diseases Group. Clin Infect Dis) 2014). We used the definitions used by the authors of the included manuscripts to provide for consistency in the comparisons. We have added some further comment to the discussion on page 16 as suggested by the reviewer.


Response: We have actioned this change now.
3.8: Minor: Flow chart indicates June 16, 2011 as last-access date. Update is necessary to include newer studies (if any).

Response: This has been updated to April 3, 2014.