Reviewer's report

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

**Version:** 2  
**Date:** 16 September 2014

**Reviewer:** Panayiotis Ziakas

**Reviewer's report:**

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.

**Major criticism**

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. 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.

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). 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 revised/updated in 2008. 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).

**Minor criticism**


Flow chart indicates June 16, 2011 as last-access date. Update is necessary to include newer studies (if any).
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

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