META-ANALYSIS

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Efficacy and safety of triazoles *versus* echinocandins in the treatment of invasive aspergillosis: A meta-analysis

Poredjenje efikasnosti i bezbednosti triazola sa ehinokandinima u lečenju invazivne aspergiloze: meta-analiza

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Abstract

Backgroun/Aim. Although majority of guidelines recommend triazoles (voriconazole, posaconazole, itraconazole and isavuconazole) as first-line therapeutic option for treatment of invasive aspergillosis, echinocandins (caspofungin, micafungin and anidulafungin) are also used for this purpose. However, head-to-head comparison of triazoles and echinocandins for invasive aspergillosis was rarely target of clinical trials. The aim of this meta-analysis was to compare efficacy and safety of triazoles and echinocandins when used for treatment of patients with invasive aspergillosis. **Methods.** This meta-analysis was based on systematic search of literature and selection of high-quality evidence according to pre-set inclusion and exclusion criteria. The literature search was made for comparison of treatment with any of triazoles (isavuconazole, itraconazole, posaconazole or voriconazole) versus any of echinocandins (caspofungin, anidulafungin or micafungin). The effects of triazoles (itraconazole, posaconazole or voriconazole) and echinocandins (caspofungin, anidulafungin or micafungin) were summarized using RevMan 5.3.5 software, and heterogeneity assessed by the Cochrane Q test and I^2 values. Several types of bias were assessed, and publication bias was shown by the funnel plot and Egger's regression. **Results.** Two clinical trials and three cohort studies were included in this meta-analysis. Mortality in patients with invasive aspergillosis who were treated with triazoles was significantly lower than in patients treated with echinocandins [odds ratio 0.29 (0.13, 0.67)], and rate of favorable response (overall treatment success) 12 weeks after the therapy onset was higher in patients treated with triazoles [3.05 (1.52, 6.13)]. On the other hand, incidence of adverse events was higher with triazoles than with echinocandins in patients treated for invasive aspergillosis [3.75 (0.89, 15.76)], although this difference was not statistically significant. **Conclusion.**Triazoles (voriconazole in the first place) could be considered as more effective and somewhat less safe therapeutic option than echinocandins for invasive aspergillosis: However, due to poor quality of studies included in this meta-analysis, definite conclusion should await results of additional, well designed clinical trials.

Key words:
aspergillosis; triazoles; echinocandins; meta-analysis.

Apstrakt

Uvod/Cilj. Iako većina vodiča preporučuje triazole (vorikonazol, itrakonazol, posakonazol i isavukonazol) kao primarnu terapijsku opciju za lečenje invazivne aspergiloze, ehinokandini (kaspofungin, mikafungin i anidulafungin) takođe se koriste u ovu svrhu. Uprkos ovoj činjenici, poređenje triazola i ehinokandina za lečenje invazivne aspergiloze retko je ispitivano u kliničkim studijama. Cilj ove meta-analize bio je da uporedi efikasnost i bezbednost triazola sa ehinokandinima kod bolesnika sa invazivnom aspergilozom. **Metode.** Ova meta-analiza je bazirana na sistematskoj pretrazi literature i biranju najkvalitetnijih studija prema uključujućim i isključujućim kriterijumima. Literatura je pretraživana za poređenje lečenja bilo kojim od triazola (isavukonazol, itrakonazol, posakonazol ili vorikonazol) naprema lečenju ehinokandinima (kaspofungin, anidulafungin ili mikafungin). Efekti triazola (itrakonazola, posakonazola i vorikonazola) i ehinokandina (kaspofungina, anidulafungina i mikafungin) sumirani su u RevMan 5.3.5 programu, a heterogenost je određena Cochrane Q testom i I^2 vrednostima. Nekoliko tipova sistematskih grešaka zbog pristrasnoti (*bias)* je ispitano, a sistematska greška u pogledu pristrasnosti u publikovanju je prikazana pomoću *funel plot*-a i Eger-ove regresije. **Rezultati.** Dve kliničke studije i tri kohortne studije bile su uključene u meta-analizu. Smrtnost kod bolesnika sa

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invazivnom aspergilozom, koji su tretirani triazolima, bila je značajno manja u poređenju sa onom kod bolsnika lečeniuh ehinokandinima [*odds ratio* 0.29 (0.13, 0.67)], i stopa povoljnog odgovora (uspeh lečenja) nakon 12 nedelja terapije bila je veća kod triazola [3.05 (1.52, 6.13)]. Sa druge strane incidencija neželjenih efekata bila je veća, ali ne statistički značajno, kod triazola nego kod ehinokandina u lečenju invazivne aspergiloze [3.75 (0.89, 15.76)]. **Zaključak.** Triazoli (pre svega vorikonazol) se mogu smatrati efikasnijom i, ponekad, manje bezbednom terapijskom opcijom nego ehinokandini za lečenje invazivne aspergiloze. Ipak, zbog slabog kvaliteta studija u ovoj meta-analizi, definitivni zaključak treba da sačeka dodatne, bolje dizajnirane studije**.**

Ključne reči:
aspergiloza; triazoli; ehinokandini; meta-analiza .

Introduction

Invasive aspergillosis (IA) is the most frequent invasive mold infection caused by fungi belonging to the genus *Aspergillus*. It is a potentially life-threatening infection (usually taking place in the respiratory tract) with high mortality rate (80–90%) in high risk patients such as patients with hematological malignancies and patients undergoing hematopoietic stem cell transplant (HSCT) [1]. Without adequate therapy, invasive pulmonary aspergillosis is further complicated as a result of hematogenous dissemination or direct extension leading to infection of other tissues, the central nervous system (CNS) or cardiovascular system [2]. IA is the most common type of infection among stem cell transplant recipients, and the second most common type of fungal infection in organ transplant recipients. One-year survival in patients with IA was 59% in organ transplant recipients [3] and 25% among recipients of stem cells [4]. A major barrier to successful treatment of IA is delayed diagnosis. Due to the lack of reliable and feasible diagnostic techniques, over one third of *Aspergillus* infections still remain undiagnosed [5]. Members of the European Organization for Research in Treatment of Cancer/Invasive Fungal Infection Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) formed a Consensus Committee in order to develop standard definitions for invasive fungal infections for clinical research [6]. According to them, three levels of certainty of IA were defined: proven, probable, and possible. From the year 2008, the same study group recommended detection of serum biomarker galactomannan as one of the criteria of probable IA, which is very much helpful when diagnosing this infection in neutropenic patients before characteristic chest radiographic (x-ray) signs of aspergillosis become visible.

There are only four major classes of antifungal agents (polyenes, flucytosine, azoles and echinocandins) which could be used for systemic treatment of invasive mycoses. Primarily, amphotericin B and flucitosine were exploited, but due to their high toxicity, triazoles as efficient and safer drugs were later on usually recommended as the first-line choice in medical literature; however this recommendation was not based on comparative studies between triazoles and echinocandins [7, 8].

Triazoles are isomeric chemical compounds containing a five-membered ring with two carbon atoms and three nitrogen atoms. These drugs (posaconazole, isavuconazole, itraconazole and voriconazole) primarily inhibit synthesis of ergosterol by inhibition of lanosterol 14α-demethylase enzymes in the fungal membrane, but not in host cells. Currently, they are successfully used in clinical management of invasive mycoses, including prophylaxis, pre-emptive, empiric and targeted therapy. On the other hand, echinocandins, which were developed in the early 2000s, are also frequently used in the treatment of invasive mycoses (including aspergillosis) due to their low host toxicity and good efficacy, especially as salvage therapy for IA [9]. Three echinocandins, caspofungin, micafungin and anidulafungin, were the first antifungals that were created to selectively target the fungal cell wall. Echinocandins cause disruption in the b-(1,3)-D-glucan synthesis and increase permeability of cell wall that leads to a disbalance of the intracellular osmotic pressure of the fungal cell and the fungal cell lysis [10].

Although clinical trials comparing triazoles and echinocandins for curing IA were published, neither meta-analysis nor systematic review were performed on this topic up to date. Summarizing the available evidence about efficacy and safety of triazoles vs. echinocandins in this indication will be helpful for planning future clinical trials or observational studies with these drugs for IA.

The aim of this meta-analysis was to compare efficacy and safety of triazoles and echinocandins when used for treatment of patients with IA.

Methods

Our study was registered at PROSPERO register of systematic reviews and meta-analyses under the number CRD42017081282 prior to commencement of the research.

The following criteria to include studies for this review were used: 1. types of studies – both randomized, controlled clinical trials and observational studies which compare any of triazoles with any of echinocandins in patients with IA; 2. types of participants – patients of both sex and any age with proven or probable IA (proven IA is characterised by documented histopathological and microbiological evidence of *Aspergillus spp*. infection, either at autopsy or in biopsied tissue or culture samples from a normally sterile site; probable IA is characterised by the presence of radiological [nodules, cavities, halos or air crescent signs on chest radiography or computed tomography (CT)] and microbiological (direct microscopy, culture) features in an immune-suppressed patient [absolute neutrophil count (ANC) < 500 cells/mm^3, prolonged steroid therapy, use of a T-cell suppressor or allogeneic stem transplantation]; 3. types of interventions – intravenous treatment with any of triazoles (isavuconazole, itraconazole, posaconazole or voriconazole) *versus* any of

echinocandins (caspofungin, anidulafungin or micafungin) for at least 7 days.

Search methods for identification of studies primarily included electronic databases, and collection of journal articles and books of University Library, University of Kragujevac, Kragujevac, Serbia. The literature search was made for comparison of treatment with any of triazoles (isavuconazole, itraconazole, posaconazole or voriconazole) *versus* any of echinocandins (caspofungin, anidulafungin or micafungin). Electronic searches of the literature were conducted in MEDLINE (PubMed, coverage from 1966 to present), Scopus/Elsevier (coverage from 1966 to present), EBSCO (Discovery Service, coverage from 1944 to present), SCINDEKS (Serbian Citation Index, coverage from 2001 to 2018), The Cochrane Central Register of Controlled Trials – CENTRAL (Wiley Online Library, coverage from 1966 to present) and a registry and results database of clinical studies of human participants ClinicalTrials. gov up to November 30, 2017. Additional searches were conducted up to March the 18th, 2018. Electronic databases were searched independently for relevant studies by two authors: SU and RŽZ. The searching strategies were presented in detail for each of the investigators in the Supplementary file. The most comprehensive strategy was used by the SU for the MEDLINE database, as following: (("voriconazole"[MeSH Terms] OR "voriconazole"[All Fields]) OR ("itraconazole" [MeSH Terms] OR "itraconazole"[All Fields]) OR ("posaconazole"[Supplementary Concept] OR "posaconazole"[All Fields]) OR ("isavuconazole"[Supplementary Concept] OR "isavuconazole"[All Fields])) AND (("aspergillosis"[MeSH Terms] OR "aspergillosis"[All Fields]) OR (invasive[All Fields] AND ("aspergillosis"[MeSH Terms] OR "aspergillosis"[All Fields]))) AND (("caspofungin"[Supplementary Concept] OR "caspofungin"[All Fields]) OR ("anidulafungin"[Supplementary Concept] OR "anidulafungin"[All Fields]) OR ("micafungin"[Supplementary Concept] OR "micafungin"[All Fields])). There were no restrictions on publication date, format or language in the search strategy. The references of the retrieved articles were searched for further similar studies ("snowball search"). The collection of journal articles and books of University Library, University of Kragujevac was hand searched for relevant studies by one author (RZZ).

Data collection and analysis

The data collection sheet was created and the articles included in the review were assessed for: 1. study identifier (ID); 2. report ID; 3. review author initials; 4. citation and contact details; 5. eligibility for review; 6. study design; 7. total study duration; 8. risk of bias (randomization if any, sequence generation, allocation sequence concealment, blinding, other concerns about bias); 9. total number of patients; 10. age of patients; 11. sex of patients; 12. settings; 13. country; 14. number of different intervention groups (triazole or echinocandin); 15. route of administration; 16. dose regimen; 17. duration of administration; 18. incidence of adverse events; 19. treatment discontinuation due to side effects; 20. mortality for each treatment group; 21. complete response at end of treatment for each treatment group; 22. partial response at end of treatment for each treatment group; 23. favorable response (overall treatment success) at 12 weeks after the start of treatment; 24. failure to respond at end of treatment; 25. failure at end of treatment; and 26. stable disease at end of treatment. Values provided as percentages were converted into actual patient numbers (n) for analysis, as well as standard errors into standard deviations using number of patients, when reported as such.

Selection of studies

Based on the searching strategy, all titles and abstracts retrieved were independently scanned by four authors (SU, RŽZ, MR and SJ). Eligibility of the retrieved articles was assessed at first from the title and the abstract, and if it was not possible, the full text of the articles was retrieved and searched. An article was included for review if all authors (SU, RŽZ, MR and SJ) agreed that eligibility criteria had been met. In case that the reviewers had different opinions about eligibility of a study for inclusion, the matter was resolved by the corresponding author (RŽZ).

Data extraction and management

The data were extracted from eligible studies using the data collection sheet described previously (under the "data collection and analysis" subheading). The data collection sheet was made in electronic form, using an Excel 2007 worksheet. The data were extracted by three investigators independently (SU, RŽZ and MR) and then collating of the four tables was done by another investigator (SJ), who produced the final extraction table. Meta-analysis was made for the following head-to-head comparisons found in the literature: itraconazole, posaconazole or voriconazole *versus* caspofungin, anidulafungin or micafungin.

Assessment of risk of bias in included studies

Risk of bias was assessed by two investigators independently (RŽZ and MR), and collating the assessments was done by the another investigator (SJ). The following sources of bias were assessed: 1. randomization if any; 2. sequence generation; 3. allocation sequence concealment; 4. blinding; 5. performance bias; 6. detection bias; 7. attrition bias; and 8. reporting bias. Although some of the studies had high risk of bias, none was excluded from further analysis due to small number of eligible studies (only five).

Measures of treatment effect

All of the outcomes used in the studies were dichotomous: mortality for each treatment group; complete response at the end of treatment for each treatment group; partial response at the end of treatment for each treatment group; favorable response (overall treatment success) at 12 weeks after the start of treatment; failure to respond at the end of

treatment; failure at the end of treatment; stable disease and adverse events frequency. For these outcomes the treatment effect was measured by risk ratio (RR).

Unit of analysis issues

Unit of analysis in the clinical trials or cohort studies that were included in this meta-analysis were individual patients. Individual participants were either randomized or simply allocated to one of two parallel intervention groups, and a single measurement for each outcome from each participant was collected and analyzed.

Dealing with missing data

Missing data were requested directly from the original investigators, however they did not respond to our requests except with courtesy. The missing data were then searched for among the results presented on ClinicalTrials.gov, when available. Finally, the potential impact of missing data on the findings of the meta-analysis will be addressed in the Discussion section.

Assessment of heterogeneity

Between-study heterogeneity was assessed with the Cochrane Q test using a χ^2 function (p values < 0.10 were considered significant). I^2 values were calculated to quantify inconsistency across studies. I^2 values of 30% or less may represent low heterogeneity, values from 30 to 50% may represent moderate heterogeneity, values from 50% to 90% substantial heterogeneity and values of 90% or more may represent considerably heterogeneity. An I^2 value > 30% was considered significant in this meta-analysis.

Assessment of reporting biases

The possibility of within-study selective outcome reporting was examined for each study included in this meta-analysis. First, by constructing matrix of the outcomes for all studies, we identified studies and specific outcomes that were not reported. Then we searched for published protocols of such studies at ClinicalTrials.gov and other forms of publications of the same studies, in order to find the missing outcomes. Finally, the authors were contacted with a request to provide the missing data, but they did not send us the data.The possibility of between-study publication bias was examined by construction of funnel plots for continuous outcomes and by the Egger's regression for discrete outcomes [11]. The Klein's number was also calculated for all outcomes [12].

Data synthesis

The random effects model (which includes both within-study and between-study variations in calculation of the weighted average) was used to combine the results from the studies. The Mantel-Haenszel method (fixed effect model) was also used to estimate how our conclusions could be influenced by assumptions about the model and by the study heterogeneity. Since significant heterogeneity of the studies was not found, subgroup analysis was not performed. All calculations were done by Review Manager (RevMan) software version 5.3.5 [13].

Sensitivity analysis

Sensitivity analysis was performed by excluding individual trials one at a time and recalculating the pooled odds ratio (OR) and mean difference estimates for the remaining studies. In this way we got insight how each of the included studies influenced our conclusions.

Results

Results of the literature search are shown in Figure 1. Only five studies fulfilled all inclusion and missed all exclusion criteria which were set prior the study commencement (two of the trials were published in the same publication, Raad et al. [14], and one trial was published in two publications [15, 16]). Characteristics of the included studies with risk of bias are shown in detail in Table 1 [14–18].

Summaries of differences in effects of triazoles vs. echinocandins for the main outcomes (using random effects model) were as following: triazoles were associated with lower mortality (OR 0.29), higher complete and partial response rate at end of treatment (ORs 2.38 and 2.83, respectively), more favorable response (overall treatment success) at 12 weeks after the start of treatment (OR 3.05), less failure to respond at the end of treatment (OR 0.38) and more stable disease at end of treatment (OR 1.16), but treatment discontinuation due to side effects and incidence of adverse events were higher with triazoles than with echinocandins (ORs 3.89 and 3.75, respectively). Details of summaries of differences in effects are shown in Table 2, expressed as RR. Sensitivity analysis did not show significant changes with exclusion of single trials.

Summaries of differences in effects of triazoles and echinocandins for the most important outcomes (mortality, complete response at the end of treatment and incidence of adverse effects) with heterogeneity estimates are shown by the Forest plots (Figures 2, 3 and 4).

The reporting bias was assessed by the Klein's number, Egger's regression and a funnel plot, using "trim and fill" method for mortality as the outcome. The central symmetry axis of a funnel plot for mortality rate did not change place significantly after "trim and fill" exercise. In Figure 5 funnel plots are shown before and after "trim and fill" exercise for mortality outcome. The Klein's number for mortality rate was 9.63, however the Egger's regression showed significant correction of the summary effect estimate: from OR = 0.29 to OR = 0.001 (Figure 6).

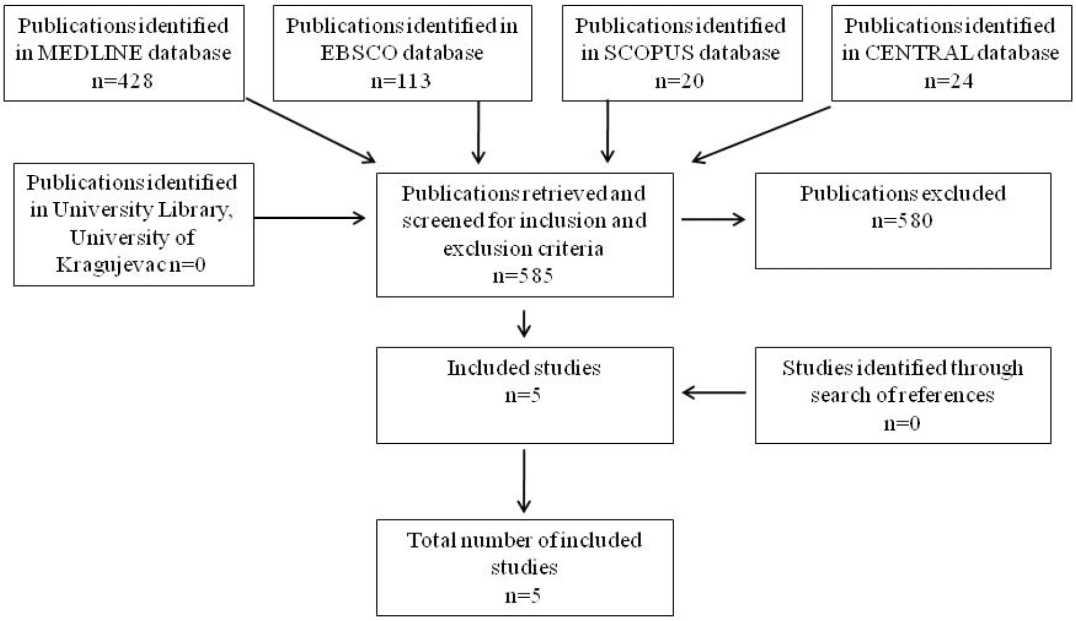

Fig. 1 – Selection of studies included in the meta-analysis.

Table 1

Characteristics of the studies included in the meta-analysis

Study	Cornely et al.[17]	Walsh et al.[16]	Raad et al.[14]	Rabagliati et al[18]	van Burik et al. [15]
Methods	Phase II, multicentre, prospective, controlled, open-label, randomized and parallel arm clinical study	A retrospective chart review (retrospective cohort study)	A retrospective chart review (retrospective cohort study)	A retrospective chart review (retrospective cohort study)	Prospective, open-label, multicenter studywith external control group*
Participants	Patients 25–76 years old with invasive aspergillosis who received treatment intravenously 300 mg once-daily (QD) intravenous micafungin monotherapy, voriconazole (6 mg/kg twice daily loading dose, followed by 4 mg/kg twice daily); or caspofungin (70 mg loading dose followed by 50 mg (QD)"	Patients in caspofungin group 22–77 years old, voriconazole group 7–81 years old and combination group 22–74 years old, with invasive aspergillosis who received intravenously 4 mg/kg voriconazole every 12 h after 6 mg/kg twice daily on the first day; a loading dose of 70 mg and 50 mg thereafter for caspofungin; or both	Patients in caspofungin group 21–77 years old, voriconazole group 24–75 years old and combination group 7–80 years old, with invasive aspergillosis who received intravenously 4 mg/kg voriconazole every 12 h after 6 mg/kg twice daily on the first day; a loading dose of 70 mg and 50 mg thereafter for caspofungin; or both	Patients in voriconazole group 47.4 ± 17.1 years old, in caspofungin group 48.1 ± 18.6 years old with invasive aspergillosis who received therapy intravenously.	Patients with invasive aspergillosis who received posaconazole orally and comparators intravenously
Interventions	Two groups, micafungin (n=12) vs. caspofungin (n=4) or voriconazole (n=1)	Primary treatment: Caspofungin (n=15), voriconazole (n=38) and combination (n=33)	Salavage therapy: Caspofungin (n=17), voriconazole (n=24) and combination (n=35)	Voriconzole (n=46) patients, caspofungin (n=51) patients	Posaconazole n = 107), control group (n = 86) [amphotericin B (any formulation), itraconazole, and/or investigational agents when the study was conducted (eg, voriconazole and echinocandins)]

Table 1 ***(continued)***

Study	Cornely et al.[17]	Walsh et al.[16]	Raad et al.[14]	Rabagliati et al[18]	van Burik et al. [15]
Outcomes	-Mortality for each treatment group; -Complete response at end of treatment for each treatment group -Favorable response (overall treatment success) at 12 weeks after the start of treatment	- Treatment discontinuation due to side effects -Mortality for each treatment group - Complete response at end of treatment for each treatment group	- Treatment discontinuation due to side effects - Mortality for each treatment group - Complete response at end of treatment for each treatment group	- Mortality for each treatment group -Complete response at end of treatment for each treatment group -Favorable response (overall treatment success) at 12 weeks after the start of treatment -Failure at end of treatment Stable disease at end of treatment	-Complete response at end of treatment for each treatment group -Partial response at end of treatment for each treatment group -Favorable response (overall treatment success) at 12 weeks after the start of treatment -Failure to respond at end of treatment -Stable disease at end of treatment
Risk of random sequence generation bias	Low: Randomized study	High: Observational design	High: Observational design	High: Observational design	High: Observational design
Risk of allocation concealment bias	Low: Randomized study	High: Observational design	High: Observational design	High: Observational design	High: Observational design
Risk of blinding of patients and personnel bias	High: There was no blinding	High: There was no blinding	High: There was no blinding	High: There was no blinding	High: There was no blinding
Risk of blinding of outcome assessment bias	High:There was no blinding of outcome assessment	High: There was no blinding of outcome assessment	High: There was no blinding of outcome assessment	High: There was no blinding of outcome assessment	Low: Measurement of all study outcomes were made by the Independent Data Review Board
Risk of incomplete outcome data bias	Low: There was no attrition bias.	Low: There was no attrition bias	Low: There was no attrition bias	Low: There was some attrition bias	High: High attrition bias, since in the micafungin group the attrition rate was 75% and in the active control group 80%
Risk of selective reporting bias	High: The authors did not pre-specify primary and secondary outcomes in the Methods section, which were later on reported in the Results	High reporting bias, as not all outcomes specified in the Methods were reported in the Results	High reporting bias, as not all outcomes specified in the Methods were reported in the Results	High: as not all outcomes specified in the Methods were reported in the Results	High: The authors did not pre-specify primary and secondary outcomes in the Methods section, which were later on reported in the Results
Risk of other bias	High: Efficacy outcomes were not reported for entire intention-to-treat population	High: Efficacy outcomes were not reported for entire intention-to-treat population	Low: Efficacy outcomes were reported for entire intention-to-treat population	Low: Efficacy outcomes were reported for entire intention-to-treat population	Low: Efficacy outcomes were reported for entire intention-to-treat population

***external control group – since a control treatment could not have been compared with posaconazole in the same study, the patients from participating study sites who were treated by the control drugs, but not enrolled in the study, were used as controls if fulfilling pre-specified criteria. The control patients were matched with patients receiving posaconazole for important prognostic factors to allow for fair comparison between the treatments.**

Table 2

Summary of findings of studies included in the meta-analysis

Triazoles (itraconazole, posaconazole and voriconazole) compared with echnocandins (caspofungin, anidulafungin or micafungin) for treatment of invasive aspergillosis						
Patient or population: both sex and any age with proven or probable invasive aspergillosis Settings: hospitalized patients. Intervention: Triazoles (itraconazole, posaconazole and voriconazole) Comparison: Echnocandins (caspofungin, anidulafungin or micafungin)						
	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Echinocandins	Triazoles				
Mortality (death rate)	33.3% 60% 53% 32%	– 11% 33% 20%	 RR 0.18 (11-60%) RR 0.62 (33-53%) RR 0.63 (20-32%)	17 (Cornely et al. [17]) 53 (Raad et al. [14], primary therapy) 41 (Raad et al. [14], salvage therapy) 97 (Rabagliati et al. [18])	⊕⊖⊖⊖very low ⊕⊕⊕⊖moderate ⊕⊕⊕⊖moderate ⊕⊕⊖⊖low	In the study of Cornely et al. the authors did not state the outcome of treatment with voriconazole.
Incidence of adverse events	25% 0.6% 5% - -	20% 18% 16% HSCT - 17% non-HSCT - 25%	RR 0.8 (20- 25%) RR 30 (0.6-18%) RR 3.2 (5-16%) - -	17 (Cornely et al. [17]) 53 (Raad et al. [14], primary therapy) 41 (Raad et al. [14], salvage therapy) 193 (Burik et al. [15], Walsh et al. [16])	⊕⊖⊖⊖very low ⊕⊕⊕⊖moderate ⊕⊕⊕⊖moderate ⊕⊕⊖⊖low	

Table 2 ***(continued)***

	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Echinocandins	Triazoles				
Complete response at end of treatment	25% 26% 29% 17.8% 9%	60% 47% 45% 65% 6%	RR 2.4 (25-60%) RR 1.8 (26-47%) RR 1.6 (29-45%) RR 3.7 (17.8-65%) RR 0.7 (6% to 9%)	17 (Cornely et al. [17]) 53 (Raad et al. [14], primary therapy) 41 (Raad et al. [14], salvage therapy) 97 (Rabagliati et al. [18]) 193 (Burik et al. [15], Walsh et al. [16])	⊕⊖⊖⊖very low ⊕⊕⊕⊖moderate ⊕⊕⊕⊖moderate ⊕⊕⊖⊖low ⊕⊕⊖⊖low	
Partial response at end of treatment	16.2%	35%	RR 2.2 (16.2-35%)	193 (van Burik et al. [15], Walsh et al.[16])	⊕⊕⊖⊖low	
Favorable response (overall treatment success) at 12 weeks after the start of treatment	50% 60.7% 26%	20% 80% 42%	RR 0.4 (20-50%) RR 1.3 (60.7-80%) RR 1.6 (26-42%)	17 (Cornely et al. [17]) 97 (Rabagliati et al. [18]) 193 (Burik [15], Walsh [16])	⊕⊖⊖⊖very low ⊕⊕⊖⊖low ⊕⊕⊖⊖low	
Failure to respond at end of treatment	60%	36%	RR 0.6 (36- 60%)	193 (Burik [15], Walsh [16])	⊕⊕⊖⊖low	

Table 2 ***(continued)***

Failure at end of treatment	-	15%	-	97 (Rabagliati et al. [18])	⊕⊕⊖⊖low	
Stable disease at end of treatment	- 8.13%	5% 10%	- RR 1.2 (8.13-10%)	97 (Rabagliati et al. [18]) 193 (Burik [15], Walsh [16])	⊕⊕⊖⊖low ⊕⊕⊖⊖low	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

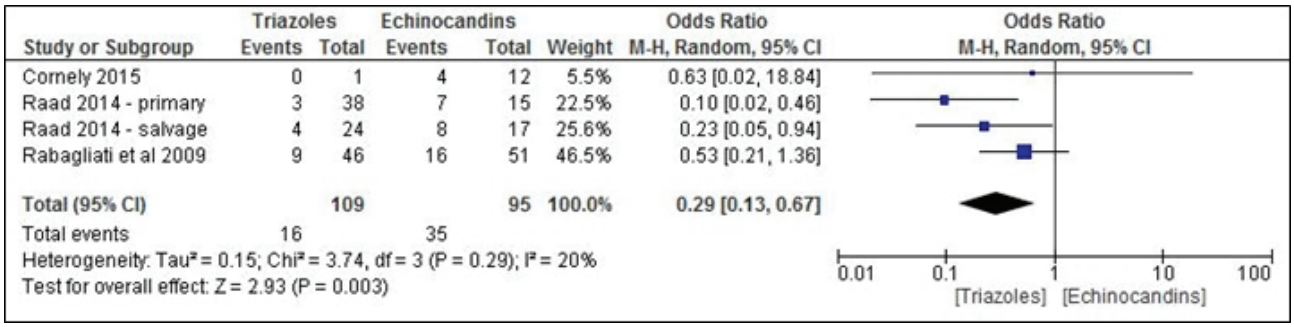

Fig. 2 – Summary of differences in mortality rate of patients with invasive aspergillosis treated by triazoles or echinocandins.
M-H – Mantel-Haenszel method; CI – confidence interval.

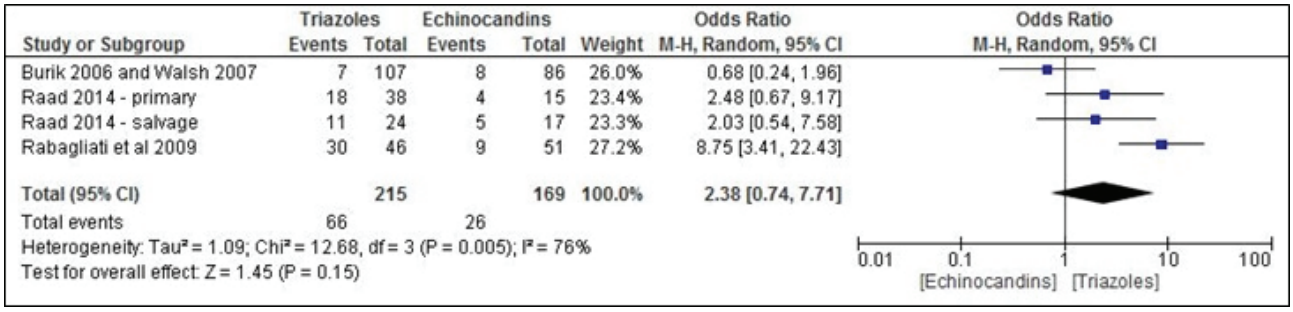

Fig. 3 – Summary of differences in complete response rate at the end of treatment of patients with invasive aspergillosis treated by triazoles or echinocandins.
M-H – Mantel-Haenszel method; CI – confidence interval.

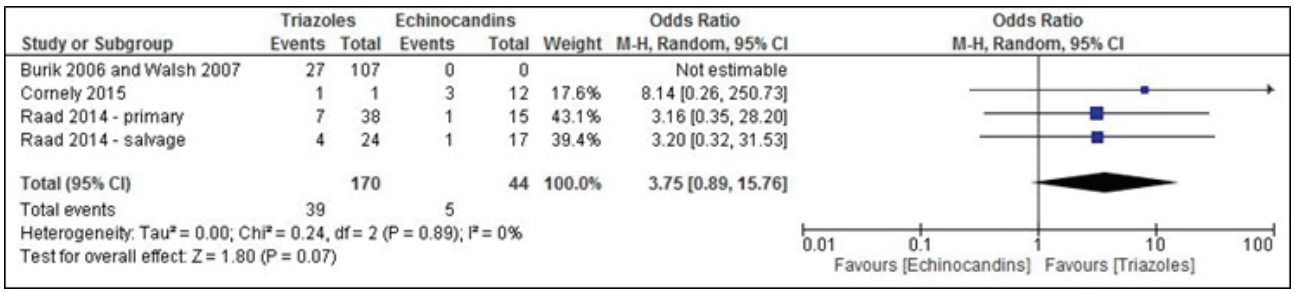

Fig. 4 – Summary of differences in adverse effects rate observed in patients with invasive aspergillosis treated by triazoles or echinocandins.
M-H – Mantel-Haenszel method; CI – confidence interval.

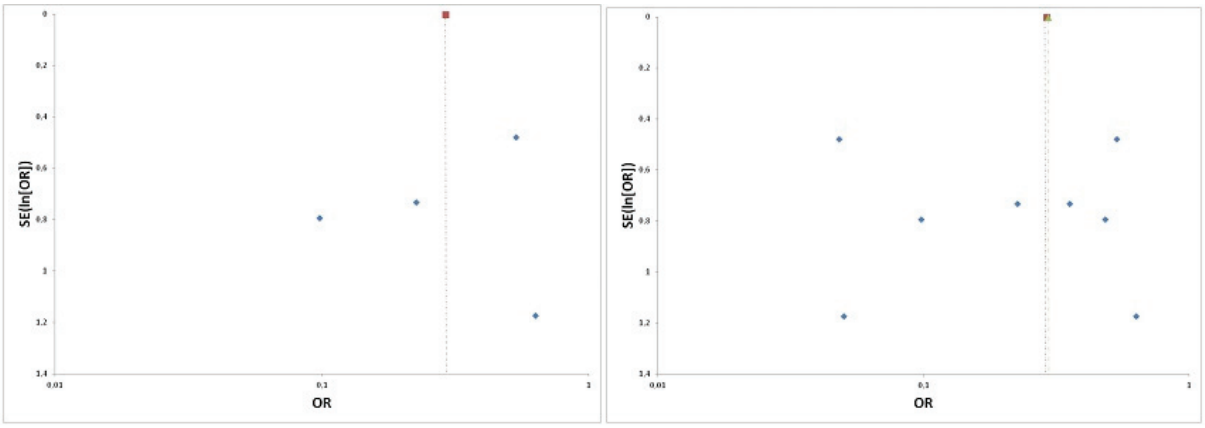

Fig. 5 – Funnel plots before and after "trim and fill" exercise for mortality rate.
OR – odds ratio; SE – standard error.

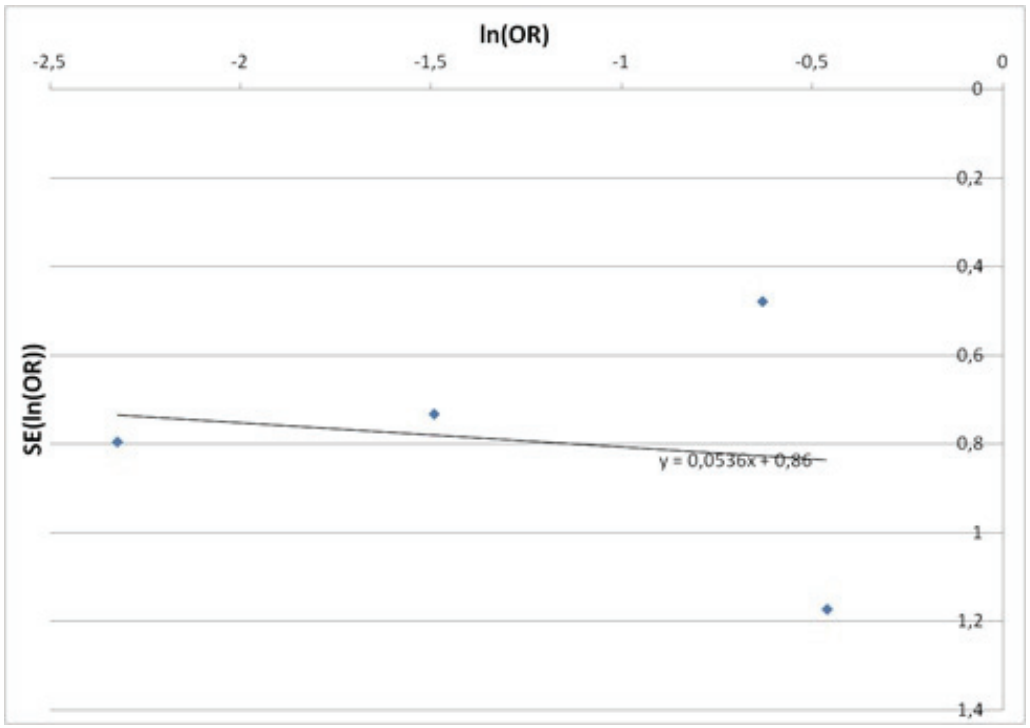

Fig. 6 – Egger's regression for mortality in the included studies.
OR – odds ratio; SE – standard error.

Discussion

Our study showed that mortality in patients with IA who were treated with triazoles was significantly lower than in patients treated with echinocandins. However, among the other efficacy outcomes, only rate of favorable response (overall treatment success) 12 weeks after the therapy onset was significantly different between the patients treated with triazoles and echinocandins, triazoles being favored. Other efficacy outcomes invariably were more beneficial in triazole groups, but significance could not be reached because not all included studies recorded every outcome, and certain of them (e.g. failure at the end of treatment or stable disease at the end of treatment) were mentioned in only one or two studies. On the other hand, incidence of adverse events was higher in groups of patients receiving triazoles.

Systematic reviews and meta-analyses of clinical studies including patients with IA are rare, and mostly focused on comparison of combination therapy (triazoles or amphotericin B plus an echinocandin) with non-echinocandin-based monotherapy (i.e.triazoles) after first-line antifungals were ineffective (salvage therapy) [19, 20]. Although authors of these studies at first concluded that combination therapy had increased efficacy, later on they questioned their own conclusions and limited it to situations where antifungal drug resistance is suspected or adequate blood levels could not be achieved [19]. Good efficacy of triazoles (mostly voriconazole) was observed in these studies, as well as relatively high rate of their adverse reactions, but triazoles and echinocandins were not compared head-to-head as monotherapy. Our meta-analysis confirmed good efficacy of triazoles against IA and relatively high adverse events rate in both first-line and salvage settings, when used as monotherapy and compared with echinocandins. Voriconazole and posaconazole penetrate to tissues to high extent (especially to lungs, voriconazole 6.26 μg/g and posaconazole 87.7 μg/mL), while among echinocandins, only anidulafungin has comparable penetration (17.9 μg/g of the lung tissue); however, in studies included in our meta-analysis, only caspofungin and micafungin were used, which could additionally explain superior efficacy of triazoles [21]. Resistance of *Aspergillus* spp. is less frequent to triazoles (from no resistance of isolated *Aspergillus* spp. to posaconazole and voriconazole, to 17% resistance of isolated *Aspergillus fumigatus* to voriconazole) [22, 23] than to echinocandins (22% resistance of *Aspergillus fumigates* to caspofungin) [23], making the first more reliable therapeutic option, especially for second-line treatment of IA.

Increased incidence of adverse events in patients with IA treated by triazoles in comparison to those treated by echnocandins that was found in our study is related mostly to increased incidence of hepatic adverse effects [24]. Although both triazoles and echinocandins may cause either hepatocellular orcholestatic liver injury, frequency is higher with voriconazole, itraconazole, posaconazole or isavuconazole than with caspofungin, anidulafungin or micafungin (up to 24% vs. up to 9%, respectively). However, majority of patients experience only laboratory abnormalities, i.e. elevation of serum levels of aspartate aminotransferase, alanine aminotransferase and bilirubin, and serious liver injuries are rare with both drug groups [24]. Our study confirmed these findings, as none of the patients exposed to either triazoles or echinocandins in included studies had fulminant hepatitis or acute liver failure, yet adverse events rate was significantly higher in groups exposed to triazoles. Additionally, all triazoles interact with cytochrome P450, especially with CYP3A4 and CYP3A5, while voriconazole interacts also with CYP2C19 [25], and their potential to inhibit elimination of other drugs metabolized through the same enzymes is much higher than that of echinocandins [26]. Echinocandins are not metabolized through cytochromes (except micafungin in minor extent) and therefore do not influence elimination of other drugs that are oxidized by these enzymes in liver [21].

Our results should be taken conditionally, since some of the important clinical outcomes were reported in only one of the included studies (e.g. failure at the end of treatment or stable disease at the end of treatment), and overall number of the included studies was low, even after widening of inclusion criteria to encompass cohort studies, which are less reliable than clinical trials due to inherent limitations of observational design. Since clinical trials with triazoles in patients with IA are likely to be initiated in close future, new meta-analysis should be made to challenge our results.

Conclusion

On the basis of published clinical trials and cohort studies triazoles (voriconazole in the first place) could be considered as more effective and somewhat less safe therapeutic option than echinocandins for invasive aspergillosis for the time being. Future studies which would include new clinical trials are necessary to confirm this conclusion.

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