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Caspofungin for prophylaxis and treatment of fungal infections in adolescents and adults: a meta-analysis of randomized controlled trials

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Background and objective: Caspofungin, a novel echinocandin compound, has been approved for the treatment of esophageal and suspected invasive candidiasis and as salvage therapy for invasive aspergillosis. The aim of this study was to assess the efficacy and safety of caspofungin for the prophylaxis and treatment of fungal infections, compared with other medications. *Methods*: PubMed, Embase, and the Cochrane Library were searched to identify relevant randomized controlled trials (RCTs) of caspofungin. Nine RCTs were included in this meta-analysis, performed using Review Manager Version 5.0. Analyses of favorable response, microbiological response, mortality rate, survival rate, relapse rate, and adverse events were performed to evaluate caspofungin. *Results:* Caspofungin produced similar effects in favorable response rate [relative risk (RR) = 1.07, 95% confidence interval (CI) 0.98–1.17], microbiological response rate (RR = 1.02, 95%CI 0.90–1.15), mortality rate (RR = 0.98, 95%CI 0.78–1.24), survival rate after 7-day follow-up (RR = 1.00, 95%CI 0.91–1.10), and relapse rate (RR = 1.18, 95%CI 0.81–1.73) compared with other antifungal agents in the prophylaxis and treatment of patients with fungal infections, particularly those caused by *Candida*. There were significant differences in clinical and laboratory adverse events between caspofungin and other antifungal agents in favor of caspofungin (RR = 0.66, 95% CI 0.49–0.89) (RR = 0.66, 95% CI 0.57–0.75). *Conclusion:* This meta-analysis shows that caspofungin can be used as effectively as other antifungal agents for prophylaxis and treatment of fungal infections, mainly for *Candida*, and that it is associated with fewer adverse effects than comparable agents.

1. Introduction

Over the past few decades, the prevalence of fungal infections has gradually increased (Bassetti et al. 2006). Many factors predispose patients to fungal infections. Recent medical advances have greatly improved the clinical outcome of major surgery, organ transplants, and cancer, with an associated increase in the prevalence and risk of fungal infections due to the immunosuppressive nature of these modern treatments (Richardson 2005). The increasing incidence of human immunodeficiency virus (HIV) infection, immunosuppressive diseases and cancer, widespread use of steroids, and indwelling central venous catheters are also significant risk factors for fungal infections (Falagas et al. 2007).

Morbidity and mortality of patients with invasive fungal infections remain high (Tortorano et al. 2004). The attributable mortality of candidemia may be as high as 47% (Wenzel 1995; Gudlaugsson et al. 2003), and this rate may be 50–90% for invasive aspergillosis. Therefore, antifungal infections remain a significant problem. Older antifungal agents are limited by their poor efficacy, significant toxicity and drug resistance. During recent years, a number of new antifungal agents have entered the market, including the echinocandins, voriconazole, and posaconazole. Several trials have studied these medications and showed positive outcomes. Of these new medications, the echinocandins are particularly appealing, because of their lower toxicity, reduced drug resistance, and strong efficacy. The echinocandins are recommended as a first-line treatment choice for invasive candidemia and suspected candidiasis, and also as salvage therapy for aspergillosis, according to the Infectious Diseases Society of America (IDSA) guidelines (Pappas et al. 2009; Walsh et al. 2008). Caspofungin, the first antifungal agent of the novel echinocandin class, was approved in 2002. It has mostly been studied in randomized clinical trials (RCTs), but there have been no comprehensive meta-analyses of caspofungin compared with other antifungal agents for fungal infections, aside from the systemic review by Falagas in 2007 (Falagas et al. 2007) who included 6 trials from 2001 to 2005. Over the past 3 years, more randomized clinical trials (RCTs) on caspofungin have been conducted, providing evaluable data on the efficacy and safety of caspofungin. We obtained the available data from RCTs to perform an overall meta-analysis to evaluate the efficacy and safety of caspofungin in the prophylaxis and treatment of fungal infections, particularly those caused by *Candida*.

2. Methods

2.1. Data sources

Two reviewers (XY and XJS) searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 4, 2009) from inception to February 2011. The search strategy was as follows: "caspofungin", "cancidas", "MK-0991", "randomized controlled trials", "clinical trial", "double-blind trial", "antifungal agents", as well as combinations of these terms. Searches were limited to RCTs. References of all identified studies were inspected for more trials.

2.2. Study selection

A study was included in this meta-analysis if: it was a RCT; it included patients with proven or probable fungal infections or those at high risk of fungal infections; it compared the efficacy and safety of caspofungin with other antifungal agents; and presented the specific data on favorable response, microbiological response, adverse effects, survival rate, relapse and mortality. Trials with blinded and non-blinded design were included. Trials only reporting dose-comparison or dosage form evaluation, experimental trials, trials focusing on pharmacokinetic or pharmacodynamic variables, and trials in pediatric patients were excluded from this meta-analysis. Trials involving caspofungin combination therapy were also excluded.

2.3. Data extraction

The same two reviewers independently extracted data from eligible trials. In case of any disagreement between the reviewers, a third reviewer extracted the data and a consensus was reached. The authors of trials were contacted for missing data when necessary. The data were extracted using a prespecified review form. The following data were extracted from each study: year of publication, number of enrolled patients and the modified intention-to-treat (MITT) patient population, clinical condition, comparator, mode and dosage of the administered treatment, favorable response after the end of treatment, microbiological response, adverse events, mortality, relapse and survival rates, trial design, treatment duration, and quality scores. The ITT patient population was defined as the patients who met the prespecified criteria for evaluation and had received the study treatment for at least 1 day. The quality of trials was assessed according to the Jadad scoring system (Jadad et al. 1996). Trials are generally considered of good quality if they have a quality score above 1.

2.4. Definition

Several definitions were used in the studied RCTs. Empirical therapy was that given to patients who had received chemotherapy for cancer or had undergone hematopoietic stem-cell transplantation or who had an absolute neutrophilic count below 500 per cubic millimeter for at least 96 h, had a fever (temperature above 38.0 °C), had received potential antibacterial therapy for at least 96 h, and did not have a documented invasive fungal infection. Treatment was considered to be prophylaxis when used to prevent high-risk patients without proven or probable fungal infections from developing such infections. Invasive candidiasis was defined as one or more positive *Candida* cultures from the blood or another sterile site before antifungal treatment. The diagnosis of oropharyngeal and esophageal candidiases referred to having endoscopically and microbiologically documented mucosal candidiasis. A favorable response for prophylaxis was defined as the completion of prophylaxis without the development of a documented invasive fungal infection during the period of prophylaxis. A favorable response for invasive candidiasis was defined as a prespecified complete or partial resolution of symptoms and signs attributable to the *Candida* infection and complete eradication of *Candida* from follow-up cultures, and a favorable response for oropharyngeal and esophageal candidiases was defined by either total clearing of esophageal lesions or a reduction in endoscopy score by more than or the equivalent of 2 grade levels. In this meta-analysis, a favorable response was evaluated at the end of antifungal therapy. Adverse events were all unintended clinical and laboratory changes, including worsening of preexisting conditions, which were temporally associated with the study drug. Survival rate was the proportion of patients who survived during the observation period after therapy. Relapse was defined as recurrence of invasive candidiasis or resumption of antifungal therapy for suspected invasive candidiasis in patients with a favorable response at the end of the intravenous study therapy during the follow-up period.

2.5. Data analysis and statistical methods

Statistical analysis was performed with Review Manager Version 5.0 (Cochrane Collaboration, Oxford, UK). The heterogeneity of trial results was assessed by the chi-square test of heterogeneity ($P < 0.10$ was taken to indicate significant heterogeneity). Publication bias was assessed by a funnel plot analysis. A fixed- effect model (FEM) was used by applying the Mantel-Haenszel method for pooling relative ratios (RRs) and 95% confidence intervals (CIs) for all outcomes throughout the meta-analysis unless statistically significant heterogeneity was found, in which case a random-effects model (REM) was used by applying the DerSimonian and Laird method.

3. Results

3.1. Study selection process

Our literature search identified 131 potentially relevant abstracts of full text articles. According to the prespecified criteria, 9 randomized trials (Wang et al. 2007; Walsh et al. 2004; Mattiuzzi et al. 2006; Mora-Duarte et al. 2002; Pappas et al. 2007; Colombo et al. 2003; Arathoon et al. 2002; Villanueva et al. 2002, 2001) involving 2901 patients were selected for this meta-analysis. Figure 1 shows the detailed screening and selection process.

3.2. Study characteristics

The main characteristics of the included trials (type of study design, characteristics of included population, drug regimen, the number of enrolled patients, Jadad score) are presented in the Table. In 6 of these trials, *Candida* was the only isolated pathogen. Eight of the nine trials were of good quality according to the Jadad scoring system and one was not (Wang et al. 2007). Three of these 9 trials were given + 3 points, 2 trials were given + 4 points, 2 trials were given + 5 points, 1 trial was given + 2 points, and 1 trial was given only + 1 point. Three of the 9 trials were performed in patients at high risk for fungal infections; 3 trials were performed in patients with proven invasive candidiasis and 3 trials in patients with oropharyngeal and/or esophageal candidiasis. Among the 9 trials, 7 were a double-blind design and 2 were open-label design. The 6 comparators used in these studies were amphotericin B (deoxycholate in 4 and liposomal in 2 RCTs), 1 was fluconazole, 1 was itraconazole, and another was micafungin. There were 3 trials with 3–4 arms, all of which included a 50-mg caspofungin arm. The common dosage of caspofungin is 50 mg daily after 70 mg the first day, so we selected the 50-mg arm compared to 1 control group. The funnel plot was examined to estimate publication bias and a symmetric inverse funnel.

Table: Main characteristics of the randomized controlled trials (RCTs) included in the meta-analysis

Study	Study design	Included population	Drug regimen		Enrolled	Intention to treat	Jadad
			Cas	Comparator	patients		Score
Wang et al. (2007)	Open-label RCT	At high risks for fungal infections	i.v. 70 mg on Day 1, then 50 mg/day	LAmB: i.v. 3 mg/kg/day	60	32 vs. 28	1
Walsh et al. (2004)	Multicenter, double-blind RCT	At high risks for fungal infections	i.v. 70 mg on Day 1, then 50 mg/day	LAmB: i.v. 3 mg/kg/day	1123	556 vs. 539	5
Mattiuzzi et al. (2006)	Open-label RCT	At high risks for fungal infections	i.v. 50 mg/day	Itraco: i.v. 200 mg, 2/d on d1∼2, followed by 200 mg/d	200	106 vs. 86	3
Mora-Duarte et al. (2002)	Multicenter, double-blind RCT	With proven invasive candidiasis	i.v. 70 mg on Day 1, then 50 mg/day	AmB: i.v. 0.6–0.7 mg/kg/ day to Non-neutropenia,i.v. 0.7–1.0 mg/kg/day to neutropenia	239	109 vs. 115	5
Pappas et al. (2007)	Multicenter, double-blind RCT	With proven invasive candidiasis	i.v. 70 mg on Day 1, then 50 mg/day	Micafungin: i.v. 100 mg/day Micafungin: i.v. 150 mg/day	595	188 vs.191 vs.199	4
Colombo et al. (2003)	Multicenter, double-blind RCT	With proven invasive candidiasis	i.v. 70 mg on Day 1, then 50 mg/day	AmB: i.v. 0.6–0.7 mg/kg/day to Non-neutropenia, i.v. 0.7–1.0 mg/kg/day to neutropenia	239	101 vs.109	2
Arathoon et al. (2002)	Multicenter, double-blind RCT	With oropharyngeal and esophageal candidiasis	i.v. 35 mg/day, i.v. 50 mg/day, i.v. 70 mg/day,	AmB: i.v. 0.5 mg/kg/day	140	34vs.34vs.35vs.35	3
Villanueva et al. (2002)	Multicenter, double-blind RCT	With esophageal candidiasis	i.v. 50 mg/day	Flu: i.v. 200 mg/day	177	81 vs. 94	4
Villanueva et al. (2001)	Multicenter, double-blind RCT	With esophageal candidiasis	i.v. 50 mg/day i.v. 70 mg/day	AmB: i.v. 0.5 mg/kg/day	128	46 vs.28 vs.54	3

Cas, caspofungin; LAmB, liposomal amphotericin B; i.v., intravenous; vs., versus; AML, acute myeloid leukemia; Itraco, itraconazole; AmB, amphotericin B; Flu, fluconazole.

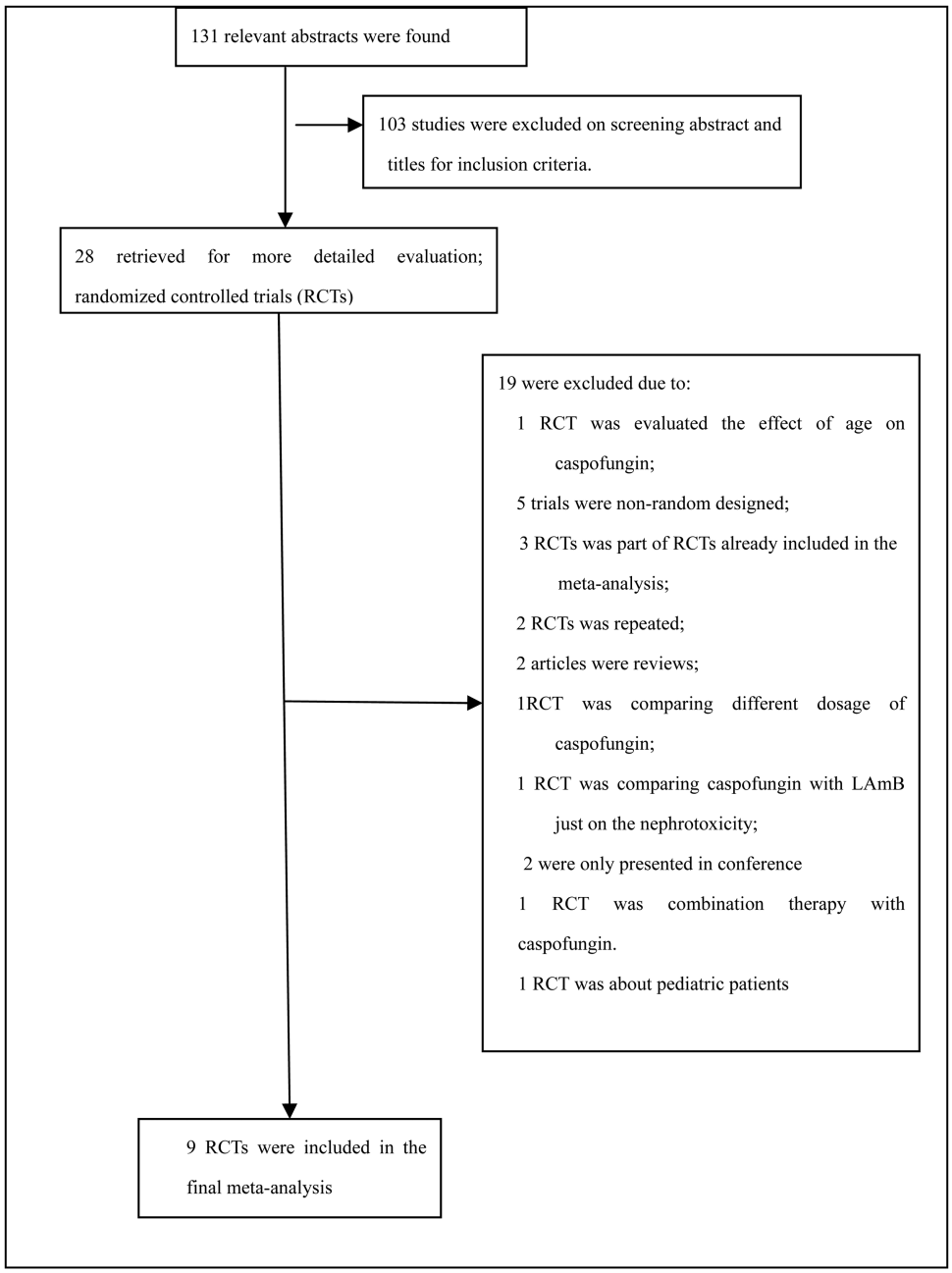

Fig. 1: Flow diagram of the randomized controlled trials (RCTs) reviewed

3.3. Clinical efficacy

Nine RCTs reported clinical favorable response rate in the MITT population. Overall, the clinical favorable response rate in the caspofungin group [693 (55.3%) of 1253 MITT patients] was similar to that in the control group [670 (53.6%) of 1251 MITT patients], and no significant difference was found (RR = 1.07, 95% CI 0.98–1.17) (Fig. 2). A similar result was confirmed in the sensitivity analysis by excluding the 2 open-label trials (2252 patients, RR = 1.09, 95% CI 0.98–1.21). There was no significant difference in survival rate after 7-day follow-up (2 trials, 1155 MITT patients, RR = 1.00, 95% CI 0.91–1.10) (Fig. 3) between caspofungin [545 (92.7%) of 588 patients] and controls [509 (89.8%) of 567 patients].

3.4. Microbiological response

Four of the 9 relevant RCTs provided microbiological treatment outcomes. *Candida* was the isolated pathogen in the 4 RCTs, mainly *Candida albicans*. In the total microbiologically evaluable population, 346 (81.6%) of the 424 patients in the caspofungin group and 366 (80.6%) of the 454 patients in the control group achieved eradication or presumed eradication of the baseline pathogens. The overall microbiological treatment success rates in the caspofungin group were not significantly different from those in the control group (878 patients, RR = 1.02, 95% CI 0.90–1.15) (Fig. 4).

3.5. Relapse rate

Three RCTs presented data on relapse rate. There was no significant difference in relapse rate between the caspofungin and control groups (571 patients, RR = 1.18, 95% CI 0.81–1.73) (Fig. 5).

3.6. Mortality rate

Three RCTs showed data on mortality in clinically assessed patients. All-cause mortality in the caspofungin group was 97/413 (23.5%), and in the control group was 103/411 (25.1%), with no significant difference between the two groups

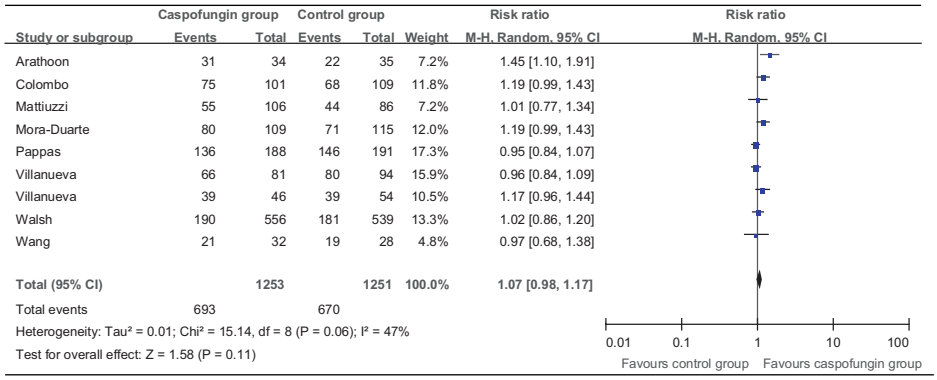

Fig. 2: Meta-analysis of favorable response comparing caspofungin with controls for the prophylaxis and treatment of fungal infections. The size of each square denotes the proportion of information given by each trial. CI = confidence interval

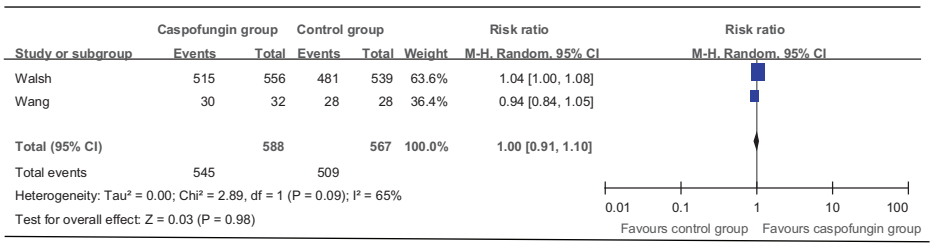

Fig. 3: Meta-analysis of survival rate after 7-day follow-up comparing caspofungin with controls for the prophylaxis and treatment of fungal infections. The size of each square denotes the proportion of information given by each trial. CI = confidence interval

(RR = 0.98, 95% CI 0.78–1.24) (Fig. 6). Moreover, the mortality attributable to fungal infections did not differ significantly between the 2 groups (RR = 0.82, 95% CI 0.34–1.96).

3.7. Adverse outcomes

The most commonly reported clinical adverse events of caspofungin were fever, chill, rash, and headache. Commonly reported laboratory adverse effects of caspofungin were an increase in alanine aminotransferase and aspartate aminotransferase and total bilirubin, and a decrease in potassium and magnesium. In this meta-analysis, 6 RCTs reported overall clinical and laboratory adverse events.

In the total evaluable safety population, 372 (44.2%) of 841 patients in the caspofungin group and 513 (60.1%) of 853 patients in the control group experienced clinical adverse events, and there was a significant difference between these 2 groups (RR = 0.66, 95% CI 0.49–0.89) (Fig. 7). There were 221 (26.4%) of 838 patients in the caspofungin group and 348 (40.8%) of 852 patients in the control group who experienced laboratory adverse events, with a significant difference between the 2 groups (RR = 0.66, 95% CI 0.57–0.75) (Fig. 8).

4. Discussion

This meta-analysis revealed that caspofungin was associated with similar effects in terms of favorable response rate, microbiological response, mortality rate, survival rate after 7-day follow-up, and relapse rate to other antifungal agents in the prophylaxis and treatment of fungal infections, mostly those caused by *Candida*. There were significant differences in clinical and laboratory adverse events between caspofungin and other antifungal agents, in favor of caspofungin.

Falagas published a systemic review of caspofungin in 2007. Six trials from 2001 through 2005 were included. This study made a meta-analysis only on some adverse effects but not on efficacy between caspofungin and comparable antifungal agents. It indicated that caspofungin appeared to be better tolerated and is at least as effective as amphotericin B for the treatment of patients with fungal infections. In our study, we conclude that caspofungin is associated with fewer adverse events than comparable antifungal agents, with no significant difference in clinical efficacy.

The first approved indication for caspofungin was salvage therapy for invasive aspergillosis. In the treatment of invasive aspergillosis, it has been shown that caspofungin can significantly prolong survival in mouse models of disseminated aspergillosis in a manner comparable to amphotericin B (Smith et al. 1996; Abruzzo et al. 1997; Bartizal et al. 1997; Abruzzo et al. 2004) and that it appeared to be at least as effective as standard therapies for patients with invasive aspergillosis (Hiemenz et al. 2001). In the selection process for this study, 3 trials on caspofungin in invasive aspergillosis were analyzed (Caillot et al. 2007; Raad et al. 2008; Singh et al. 2006), but

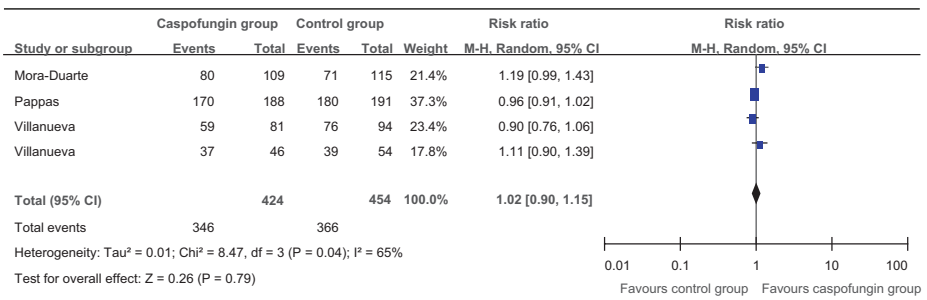

Fig. 4: Meta-analysis of microbiological treatment success rate comparing caspofungin with controls for the prophylaxis and treatment of fungal infections. The size of each square denotes the proportion of information given by each trial. CI = confidence interval

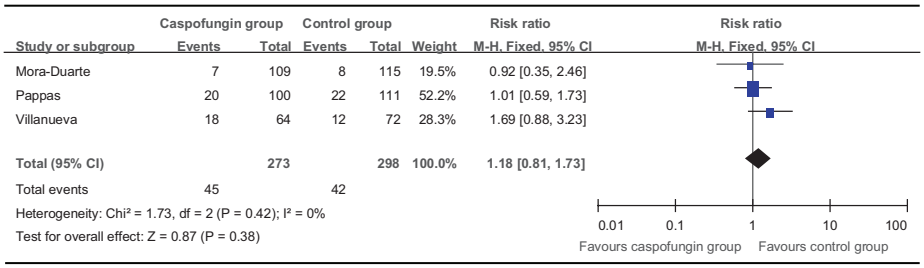

Fig. 5: Meta-analysis of relapse rate comparing caspofungin with controls for the prophylaxis and treatment of fungal infections. The size of each square denotes the proportion of information given by each trial. CI = confidence interval

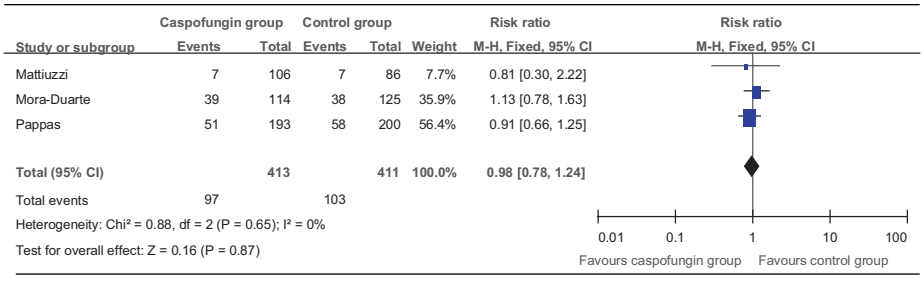

Fig. 6: Meta-analysis of all-cause mortality comparing caspofungin with controls for the prophylaxis and treatment of fungal infections. The size of each square denotes the proportion of information given by each trial. CI = confidence interval

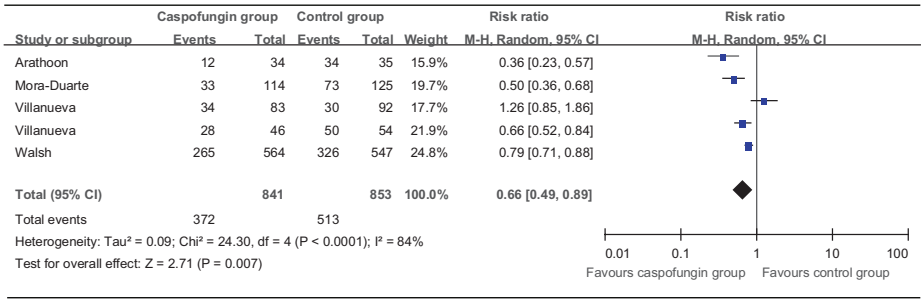

Fig. 7: Meta-analysis of clinical adverse events comparing caspofungin with controls for the prophylaxis and treatment of fungal infections. The size of each square denotes the proportion of information given by each trial. CI = confidence interval

were excluded as the trials involved combination therapy with caspofungin. These 3 trials showed that caspofungin combination therapy was more efficient than liposomal amphotericin B monotherapy for invasive aspergillosis. Until now, there have been no RCTs of caspofungin as monotherapy or as primary therapy for the treatment of invasive aspergillosis, which may be, at least in part, due to the fact that the echinocandins are fungistatic against *Aspergillus* spp., but not fungicidal.

Caspofungin is also licensed for the treatment of candidiasis and empirical antifungal therapy of presumed fungal infections in patients with febrile neutropenia (Bal 2010). In this study, most of the fungal pathogens were *Candida*. The 2004 Infectious Diseases Society of America treatment guidelines recommend caspofungin, fluconazole (for patients not previously exposed to azoles), amphotericin B, or fluconazole–amphotericin B combination therapy for initial treatment of common forms of invasive candidiasis, all with the same level of evidence and recommendation. In this study, caspofungin was compared with amphotericin B in 2 RCTs for patients with invasive candidiasis. Our analysis indicated that caspofungin was at least as effective as amphotericin B for invasive candidiasis. In 3 RCTs for patients with oropharyngeal and/or esophageal candidiasis, caspofungin was also shown to be as effective as amphotericin B and fluconazole.

Several limitations of the relevant trials should be acknowledged. First, the quality of the trials may affect the conclusion of this meta-analysis. Two of the 9 trials were not blinded, and 1 trial was assessed to be of low quality. Nevertheless, a sensitivity analysis was performed including only trials that were of high quality or that were double-blinded, resulting in find-

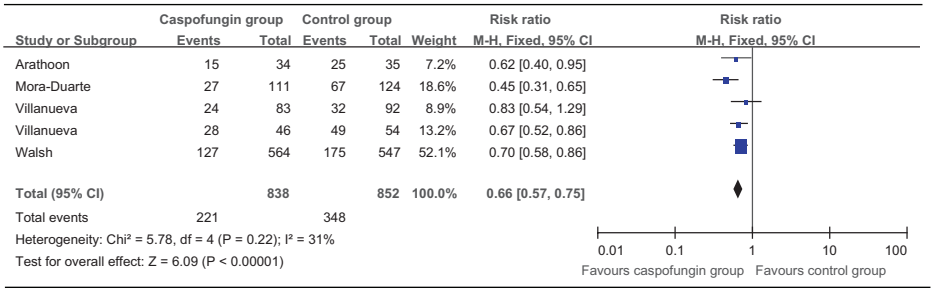

Fig. 8: Meta-analysis of laboratory adverse events comparing caspofungin with controls for the prophylaxis and treatment of fungal infections. The size of each square denotes the proportion of information given by each trial. CI = confidence interval

ings consistent with those of the primary analysis. Second, the number of studies on relapse rate and survival rate was small which may have biased the conclusion. Third, there were differences among the studies regarding the dosage of administered antifungal agents, the duration of treatment and the period of observation. There was some heterogeneity among the trials, and random-effects model was used several times, which required careful interpretation of the conclusion. Fourth, the study lacked an assessment of caspofungin for the treatment of invasive aspergillosis, so the meta-analysis regarding caspofungin treatment does not provide a complete picture.

In conclusion, despite the above limitations, this review represents the largest meta-analysis of caspofungin for antifungal therapy to date. Caspofungin was as effective as other antifungal agents in the prophylaxis and treatment of fungal therapy, mainly for Candida, while it was associated with fewer adverse drug events than other antifungal medications. However, more RCTs are needed to confirm the above conclusion.

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References

Abruzzo GK, Flattery AM, Gill CJ, Kong L, Smith JG, Pikounis VB, Balkovec JM, Bouffard AF, Dropinski JF, Rosen H, Kropp H, Bartizal K. (1997) Evaluation of the echinocandin antifungal MK-0991(L-743,872): efficacies in mouse models of disseminated aspergillosis, candidiasis, and cryptococcosis. Antimicrob Agents Chemother 41: 2333–2338.

Abruzzo GK, Gill CJ, Flattery AM, Kong L, Leighton C, Smith JG, Pikounis VB, Bartizal K, Rosen H (2000) Efficacy of the echinocandin caspofungin against disseminated aspergillosis and candidiasis in cyclophosphamide-induced immunosuppressed mice. Antimicrob Agents Chemother 44: 2310–2318.

Arathoon EG, Gotuzzo E, Noriega LM, Berman RS, DiNubile MJ, Sable CA (2002) Randomized, double- blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiases. Antimicrob Agents Chemother 46: 451–457.

Bal AM (2010) The echinocandins: three useful choices or three too many? Int J Antimicrob Agents 35: 13–18.

Bartizal K, Smith JG, Gill CJ, et al. (1997) Preclinical efficacy of MK-0991 in pancytopenic mouse models of disseminated candidiasis and aspergillosis. 37th interscience Conference on Antimicrobial Agents and Chemotherapy. F-80.

Bassetti M, Righi E, Costa A, Fasce R, Molinari MP, Rosso R, Pallavicini FB, Viscoli C (2006) Epidemiological trends in nosocomial candidemia in intensive care. BMC Infect Dis 6: 21.

Caillot D, Thiébaut A, Herbrecht R, de Botton S, Pigneux A, Bernard F, Larché J, Monchecourt F, Alfandari S, Mahi L (2007) Liposomal amphotericin B in combination with caspofungin for invasive aspergillosis in patients with hematologic malignancies. Cancer 110: 2740–2746.

Colombo AL, Perfect J, DiNubile M, Bartizal K, Motyl M, Hicks P, Lupinacci R, Sable C, Kartsonis N (2003) Global distribution and outcomes for *Candida* species causing invasive candidiasis: results from an international randomized double-blind study of caspofungin versus amphotericin B for the treatment of invasive candidiasis. Eur J Clin Microbiol Infect Dis 22: 470–474.

Falagas ME, Ntziora F, Betsi GI, Samonis G (2007) Caspofungin for the treatment of fungal infections: a systematic review of randomized controlled trials. Int J Antimicrob Agents 29: 136–143.

Gudlaugsson O, Gillespie S, Lee K Vande Berg J, Hu J, Messer S, Herwaldt L, Pfaller M, Diekema D (2003) Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 37: 1172–1177.

Hiemenz J, Raad I, Boogaerts M, et al. (2001) Efficacy of caspofungin as salvage therapy in invasive aspergillosis compared to standard therapy in a historical cohort. Focus on Fungal Infections II: 022.

Jadad A, Moore A, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17: 1–12.

Mattiuzzi GN, Alvarado G, Giles FJ, Ostrosky-Zeichner L, Cortes J, O'brien S, Verstovsek S, Faderl S, Zhou X, Raad II, Bekele BN, Leitz GJ, Lopez-Roman I, Estey EH (2006) Open-label, randomized comparison of itraconazole versus caspofungin for prophylaxis in patients with hematologic malignancies. Antimicrob Agents Chemother 50: 143–147.

Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, Lupinacci R, Sable C, Kartsonis N, Perfect J (2002) Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 347: 2020–2029.

Pappas PG, Rotstein CM, Betts RF, Nucci M, Talwar D, De Waele JJ, Vazquez JA, Dupont BF, Horn DL, Ostrosky-Zeichner L, Reboli AC, Suh B, Digumarti R, Wu C, Kovanda LL, Arnold LJ, Buell DN (2007) Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 45: 883–893.

Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD (2009) Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 48: 503–535.

Raad II, Hanna HA, Boktour M, Jiang Y, Torres HA, Afif C, Kontoyiannis DP, Hachem RY (2008) Novel antifungal agents as salvage therapy for invasive aspergillosis in patients with hematologic malignancies: posaconazole compared with highdose lipid formulations of amphotericin B alone or in combination with caspofungin. Leukemia 22: 496–503.

Richardson MD (2005) Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother 56 (Suppl 1): i5–i11.

Singh N, Limaye AP, Forrest G, Safdar N, Muñoz P, Pursell K, Houston S, Rosso F, Montoya JG, Patton P, Del Busto R, Aguado JM, Fisher RA, Klintmalm GB, Miller R, Wagener MM, Lewis RE, Kontoyiannis DP, Husain S (2006) Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. Transplantation 81: 320–326.

Smith JG, Abruzzo CJ, Flattery AM, et al. (1996) Evaluation of pneumocandin L-743872 in neutropenic mouse models of disseminated candidiasis and aspergillosis. 36th Interscience Conference on Antimicrobial Agents and Chemotherapy F-41.

Tortorano AM, Peman J, Bernhardt H, Klingspor L, Kibbler CC, Faure O, Biraghi E, Canton E, Zimmermann K, Seaton S, Grillot R (2004) Epidemiology of candidemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis 23: 317–322.

Villanueva A, Arathoon EG, Gotuzzo E, Berman RS, DiNubile MJ, Sable CA (2001) A randomized double-blind Study of caspofungin versus amphotericin for the treatment of candidal oesophagitis. Clin Infect Dis 33: 1529–1535.

Villanueva A, Gotuzzo E, Arathoon EG, Noriega LM, Kartsonis NA, Lupinacci RJ, Smietana JM, DiNubile MJ, Sable CA (2002) A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. Am J Med 113: 294–299.

Walsh TJ, Teppler H, Donowitz GR, Maertens JA, Baden LR, Dmoszynska A, Cornely OA, Bourque MR, Lupinacci RJ, Sable CA, dePauw BE (2004) Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. N Engl J Med 351: 1391–1402.

Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Segal BH, Steinbach WJ, Stevens DA, van Burik JA, Wingard JR, Patterson TF (2008) Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 46: 327–360.

Wang J, Sun A-N, Wu D-P, et al. (2007) Comparison of caspofungin and liposomal amphotericin B for empirical antifungal therapy in patients with hematologic disease. Zhongguo Kang Sheng Su Za Zhi 32: 316–319.

Wenzel RP (1995) Nosocomial candidemia: risk factors and attributable mortality. Clin Infect Dis 20: 1531–1534.