Original Article

Efficacy of combination therapy of triazole and echinocandin in treatment of invasive aspergillosis: a systematic review of animal and human studies

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Objective: The effectiveness of the combination therapy of triazole and echinocandin in treatment of invasive aspergillosis (IA) remains controversial. The objective of this systematic review was to assess the efficacy of combination therapy of triazole and echinocandin in treatment of IA.

Methods: Relevant articles on the combination therapy of triazole and echinocandin in IA, including the animal studies and clinical studies from January 1966 to October 2013, were searched on Web of Science, PubMed and Cochrane Library. The prolongation of survival of the combination therapy of triazole and echinocandin in IA was performed as risk ratio (RR) with 95% confidence interval (95% CI).

Results: Nine animal studies with a total of 1,582 animals and five clinical trials totaling 872 patients were included. The survival of the included animal studies with combination therapy was significantly prolonged compared with echinocandin alone [RR =2.26, (95% CI, 1.79-2.87; P<0.00001)], but no statistical difference compared with monotherapy of triazole [RR =1.19, (95% CI, 0.98-1.44; P=0.08)]. Of the four human cohort studies, two studies observed that the combination therapy of triazole and echinocandin was associated with a significant reduction in mortality compared with other treatments, and one study might be considered as a preferable therapy [HR =0.58, (95% CI, 0.3-1.14; P=0.117)]. While another study revealed that there was no significant difference among the combination therapy of triazole and echinocandin and either of the monotherapy. In the randomized clinical trial (RCT), of the 135 patients who received the combination therapy, 39 died, while 55 died out of 142 patients who received monotherapy (P=0.08, 95% CI, –21.4, 1.09) by week 12.

Conclusions: The combination therapy of triazole and echinocandin in treating IA results in a trend towards improved overall survival in animals' studies and clinical studies. Well-designed RCTs and further improved clinical trials are necessary to study the effectiveness of the combination therapy.

Keywords: Triazole; echinocandin; invasive aspergillosis (IA); systematic review

Submitted Dec 07, 2013. Accepted for publication Jan 06, 2014.
doi: 10.3978/j.issn.2072-1439.2014.01.18
Scan to your mobile device or view this article at: http://www.jthoracdis.com/article/view/2034/2697

Introduction

Invasive aspergillosis (IA) is an opportunistic infection caused by fungi of the genus *Aspergillus*. Due to increasing number of people with compromised immunity (most as a results of AIDS and organ transplantation), IA has been on a sharp rise for the past few decades. *Aspergillus fumigatus* is widely present in environment and the most common species recovered from cases of IA among which 90% are involved into the lung (1). Other commonly recovered species are *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*.

Invasive pulmonary aspergillosis (IPA) is a life-threatening infection associated with severe mortality. Voriconazole is considered to be the primary therapy for IPA based on the results of randomized clinical trials (RCTs) (2,3) and alternatives are liposomal amphotericin B, amphotericin B lipid complex, caspofungin, micafungin, posaconazole and

itraconazole. Despite these treatment options, the outcomes of IPA remain poor, with mortality rates of 25% to 35% 12 weeks after diagnosis (4).

The target of triazole is at cell-membrane, and the target of echinocandin is at cell-wall (2), so that the combination therapy of triazole and echinocandin may result in synergistic function against *Aspergillus spp*. strains with a wider spectrum of efficacy and lower toxicity (5-7). However, some studies showed that the combination therapy of triazole and echinocandin did not significantly improve the therapeutic outcome (8), or they might even be potentially antagonistic to each other (9). Furthermore, the combination of antifungal drugs for primary therapy of IPA is not routinely recommended by the Infectious Diseases Society of America due to lack of enough clinical data (2). Therefore, our objective was to evaluate the evidences for the combination therapy of triazole and echinocandin in treatment of IA in animal and clinical studies.

Materials and methods

Literature search

Relevant articles from January 1966 to October 2013 were searched on Web of Science, PubMed and Cochrane Library by two researchers. Keywords or text words in medical subjects heading (MeSH) included: "invasive aspergillosis" OR "invasive pulmonary aspergillosis", "triazole" OR "itraconazole" OR "voriconazole" OR "posaconazole" OR "ravuconazole", "echinocandin" OR "caspofungin" OR "micafungin" OR "anidulafungin". We also did hand searching of reviews, guidelines and citations of all included studies for complete references.

Selection criteria for studies

Animal studies

Inclusion criteria: animal models were in line with IA standard. Appropriate control groups were set, and uniform evaluation indexs were included.

Exclusion criteria: any study which was only related to pharmacokinetic study, combination of triazole or echinocandin with amphotericin B, not set with a blank or a placebo-control or repeatedly published data, was excluded.

Clinical studies

Inclusion criteria: any study in which IA was diagnosed according to the European Organization for Research and Treatment of Cancer and the Mycoses Study Group consensus criteria was included (10). We included studies in which patients were diagnosed with either proven or probable IA. We included cohort or RCT studies that assessed the efficacy of combination therapy of triazole and echinocandin with appropriate control groups.

Exclusion criteria: any study with only a case report or repeatedly published data, without control group or lacking uniform diagnostic criteria, was excluded.

Data extraction

Two reviewers independently applied selection criteria, performed quality assessment, and extracted data, including the sample size, antifungal dose, duration of treatment (days), the observed indicators and evaluation criteria. If we found that the information provided in a literature is not comprehensive, we contacted the author to get detailed information. Disagreement on whether some specific studies should be included into this study between the two reviewers was attempted to be reached a consensus in a subsequent discussion between the two reviewers, which otherwise was resolved by a third researcher.

Study quality assessment

A quality assessment of all selected full-text articles of animal studies was performed according to the ARRIVE guidelines (11,12). The Newcastle-Ottawa Quality Assessment Scales (13) for cohort clinical studies was applied to assess selection bias, comparability of exposed and unexposed groups of each cohort, outcome assessment, and attrition bias. The quality of the RCT was assessed according to modified Jadad score (14), including details of randomization, generation of random numbers, implementation of double-blinding, information on withdrawals, and allocation concealment. Two reviewers independently evaluated these components of the scale. Disagreements among reviewers were resolved by discussion until a consensus was reached.

Statistical methods and data analysis

The survival was reported as risk ratio (RR) with 95% confidence interval (95% CI). A heterogeneity test was performed to examine the homogeneity. If there was homogeneity, the fixed-effect model was used; if there was heterogeneity, the random-effect model was used. Z-statistic test for over effect was done, $P \leq 0.05$ was considered to

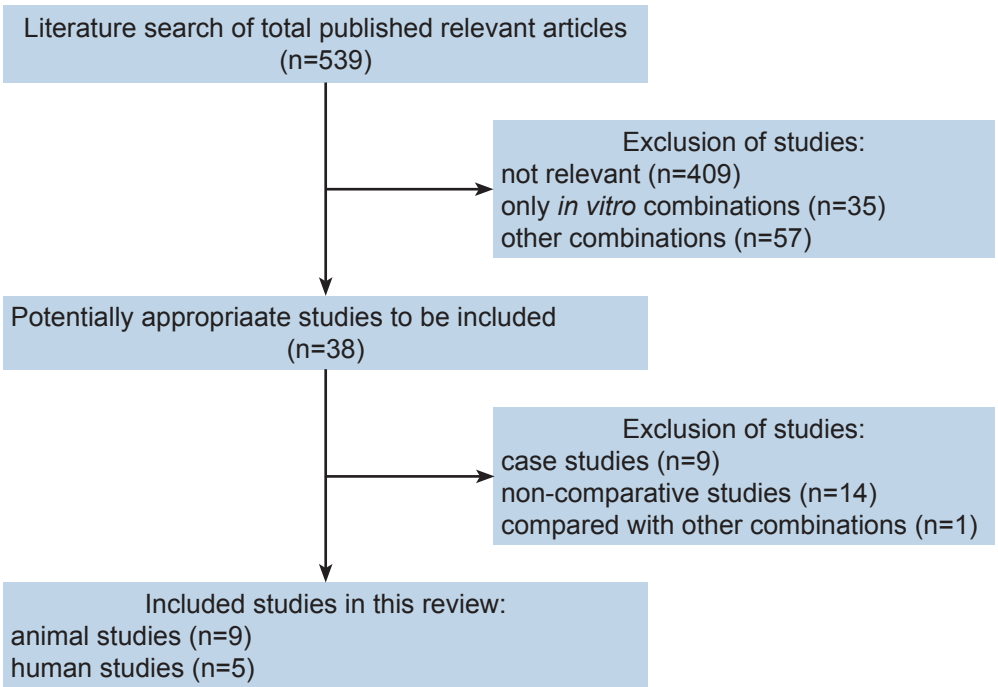

Figure 1 Flow chart of included and excluded studies.

Table 1 Quality assessment of combination therapy in animal models (Kilkenny *et al*. 2010a)

Studies	Items																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Kirkpatrick WR *et al.*, 2002 (7)	1	2	1	1	0	1	0	1	0	1	1	2	2	0	2	2	0	2	1	2
Luque JC *et al.*, 2003 (6)	1	1	1	1	0	1	1	1	0	1	1	2	2	0	2	2	0	1	0	2
Petraitis V *et al.*, 2003 (5)	1	2	2	1	0	1	1	1	0	1	1	2	2	0	2	2	0	1	1	2
MacCallum DM *et al.*, 2005 (15)	1	2	1	1	0	1	1	1	0	1	1	2	2	0	2	2	0	1	0	1
Clemons KV *et al.*, 2006 (9)	1	2	1	1	0	1	0	1	0	1	1	2	2	0	2	2	0	1	0	1
van de Sande WW *et al.*, 2009 (8)	1	2	1	1	0	1	0	1	0	1	1	2	2	0	2	2	0	1	0	1
Petraitis V *et al.*, 2009 (16)	1	2	1	1	0	1	1	1	0	1	1	2	2	0	2	2	0	1	0	2
Calvo E *et al.*, 2012 (17)	1	2	1	1	0	1	1	1	0	1	1	2	2	0	2	2	0	1	1	2
Seyedmousavi S *et al.*, 2013 (18)	1	2	1	1	0	1	0	1	0	1	1	2	2	0	2	2	0	1	0	2

be statistically significant. All statistical analyses were performed using Review Manager Version 5.1 (The Nordic Cochrane Centre, Cochrane Collaboration, 2011) software.

Results

Database searched results

The search process, the number of initially searched studies, and the number of excluded studies are illustrated in *Figure 1*. Nine animal studies (5-9,15-18) and five clinical studies, including one RCT and four cohort studies (19-24) were eligible for final review. *Tables 1* and *2* show that the included studies were of high quality. The Jadad scale score of the RCT was five.

Animal study characteristics

The main characteristics of the analyzed animal studies are summarized in *Table 3*. The survival of the included

Table 2 Newcastle-Ottawa quality assessment scale for cohort studies included in this review

Studies	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of Interest not present at start of study		Assessment of outcome	Adequacy of duration of follow-up	Adequacy of completeness of follow-up	
Marr KA *et al.*, 2004 (19)	A	A	A	A	A	B	A	A	7
Singh N *et al.*, 2006 (20)	A	A	A	A	A	B	A	A	7
Upton A *et al.*, 2007 (21)	A	A	A	A	A	B	A	A	7
Rieger CT *et al.*, 2008 (22)	A	A	A	A	A	B	A	A	7

animal studies with combination therapy was significantly prolonged compared with echinocandin alone [67.3% versus 28.9%; RR =2.26, (95% CI, 1.79-2.87; P<0.00001); *Figure 2*], but no statistical difference compared with triazole alone [67.2% versus 52.3%; RR =1.19, (95% CI, 0.98-1.44; P=0.08); *Figure 3*].

IA models infected by *A. fumigatus* (8,16,18) or *A. flavus* (17) were treated with combination therapy of voriconazole and anidulafungin or either of monotherapy of voriconazole or anidulafungin. The efficacy of the combination therapy was synergistic compared with either of the monotherapy (16-18) (survival, P<0.05). Meanwhile, Petraitis *et al*. (16) concluded that anidulafungin at a dosage of 10 mg/kg/day was antagonistic to voriconazole. Seyedmousavi *et al*. (18) showed that the combination therapy was additive in treatment of voriconazole-resistant IA. However, Van de Sande *et al*. (8) showed that the monotherapy of voriconazole was therapeutically effective and superior to the monotherapy of anidulafungin and that the combination therapy did not significantly improve the therapeutic outcome of either of the monotherapy.

Combination therapy of voriconazole and caspofungin in male Guinea pig IA model was demonstrated to be highly effective compared with caspofungin monotherapy, but no differences compared to voriconazole (7). However, another study showed highly effective (15) (survival, P=0.048). Combination therapy of itraconazole and micafungin in female mice IA model significantly improved the efficacy in prolonging survival compared with either of the monotherapy of micafungin (6), while traconazole and micafungin might be antagonistic to each other (9). Petraitis *et al*. (5) found that combination therapy of ravuconazole and micafungin might increase efficacy, sparing toxicity, or both (P<0.05).

Human study characteristics

A summary of the human study characteristics included in this review is presented in *Table 4*. The sample sizes of the reviewed human studies varied widely [47-405]. Five of the studies had treatment duration of 12 weeks or 90 days and used mortality as the endpoint.

Four studies (19-22) compared the combination therapy of voriconazole and caspofungin with voriconazole, caspofungin, or lipid formulation of amphotericin B. Marr *et al*. (19) found lower mortality in the combination therapy of voriconazole and caspofungin than monotherapy of voriconazole. Rieger *et al*. (22) showed that the mortality at the end of treatment of the combination of voriconazole and caspofungin and other treatment was 11% and 34% three months after initiation of combination therapy. Meanwhile, Singh *et al*. (20) considered that the combination therapy of voriconazole and caspofungin might be a preferable therapy. However, Upton *et al*. (21) did not observe any significant difference between this combination therapy and either of the monotherapy.

In the RCT (24), 277 patients enrolled from 93 sites in 24 countries were randomised to receive either voriconazole plus placebo (monotherapy) or voriconazole plus anidulafungin (combination therapy). Of the 135 patients who received this combination therapy, 26 (19.3%) died by week 6, compared to 39/142 (27.5%) recipients receiving either of the monotherapy (P=0.09; 95% CI, –18.99, 1.51); 39 (28.9%) died by week 12, compared to 55/142

Table 3 Characteristics of included animal studies

Studies	Types of animals	Sample sizes	Aspergillus	MIC (μg/mL)	Infective doses	Treatments		Duration of treatment (days)	Findings
						Combination therapy	Monotherapy		
Kirkpatrick WR *et al.*, 2002 (7)	Male guinea pigs	72	A. fumigatus	VRC 0.5, CAS 32	1×10^6 conidia	CAS 1 or 2.5 mg/kg/day IP + VRC 5 mg/kg/day PO	CAS 1 or 2.5 mg/kg/day IP or VRC 5 mg/kg/day PO	5	Mortality↓ (P<0.0025 compared to CAS); no differences compared to VRC
Luque JC *et al.*, 2003 (6)	Female mice	40	A. fumigatus	ITZ 1.56, MICA >16	8×10^6 conidia	MICA 3 mg/kg q12h + ICZ 100 mg/kg/day	MICA 3 mg/kg q12h or ICZ 100 mg/kg/day or no drug	12	Survival↑ (P<0.05 compared to MICA); no differences compared to ICZ
Petraitis V *et al.*, 2003 (5)	Female rabbits	36	A. fumigatus	RAV 1.0, MICA 0.25	1×10^8-1.25×10^8 conidia	MICA 1 mg/kg/day IV + RAV 2.5 mg/kg/day IV	MICA 1 mg/kg IV or RAV 2.5 mg/kg IV or no drug	12	Mortality↓ (P≤0.001); residual fungal burden↓ (P≤0.05); galactomannan indexes↓ (P≤0.01)
MacCallum DM *et al.*, 2005 (15)	Male Guinea pigs	90	A. fumigatus	VRC 0.032 to 0.5, CAS 0.125	10^4 or 10^3 conidia/g	CAS 1 mg/kg/day IP + VRC 1 mg/kg PO q12h	VRC 1 mg/kg PO q12h or CAS 1 mg/kg/day IP	7	Survival↑ (P=0.048 compared to CAS with 10^3 conidia/g)
Clemons KV *et al.*, 2006 (9)	Female mice	40	A. fumigatus	NR	3.96×10^4 conidia	MICA 1 mg/kg/day + ICZ 100 mg/kg/day	MICA 1 mg/kg/day or ICZ 100 mg/kg/day or no drug	10	Survival↓ (P>0.05)
van de Sande WW *et al.*, 2009 (8)	Female rats	58	A. fumigatus	NR	NR	AFG 20 mg/kg/day on day 1, followed 5 mg/kg/day + VRC 7.5, 10, 12.5, and 15 mg/kg on days 0, 1, 2, and 3 and 17.5 mg/kg on day 4 and beyond, IP q12h	AFG or VRC or no drug	5-10	Survival↓ (P=0.3290); galactomannan indexes (P=0.0238 and P=0.0357)

Table 3 (*continued*)

Table 3 (*continued*)

Studies	Types of animals	Sample sizes	Aspergillus	MIC (μg/mL)	Infective doses	Treatments		Duration of treatment (days)	Findings
						Combination therapy	Monotherapy		
Petraitis V *et al.*, 2009 (16)	Female rabbits	70	A. fumigatus	VRC 0.5 to 1.0, AFG 0.25	1.0×10^8-1.25×10^8 conidia	AFG 5 or 10 mg/kg/day IV + VRC 10 mg/kg q8h IV	AFG 5 or 10 mg/kg/day IV or VRC 10 mg/kg q8h IV or no drug	12	Survival↑ (P<0.001) (AFG 5 mg/kg/day); survival↓ (P>0.05) (AFG 10 mg/kg/day); residual fungal burden↓ (P<0.05); galactomannan indexes↓ (P<0.05)
Calvo E *et al.*, 2012 (17)	Male mice	240	A. flavus	VRC 0.5 to 1.0, AFG > 32	8×10^3 CFU	AFG 1 mg/kg/day IP + VRC 12.5 mg/kg PO q12h	AFG 1 mg/kg/day IP or VRC 12.5 mg/kg PO q12h or no drug	7	Survival↑ (P<0.05); residual fungal burden↓ (P<0.05); galactomannan indexes↓ (P<0.05)
Seyedmousavi S *et al.*, 2013 (18)	Female mice	882	VRC-S and VRC-R A. fumigatus	VRC 0.25 and 4, AFG 0.031	2.4×10^7 and 2.5×10^7 conidia	AFG 20 mg/kg/day + VRC 20 mg/kg	AFG 10 mg/kg/day or VRC 20 mg/kg	7	Synergistic in VRC-S; additive in VRC-R

AFG, anidulafungin; AMB, amphotericin B; CAS, caspofungin; ICZ, itraconazole; L-AMB, liposomal amphotericin B; MICA, micafungin; POC, posaconazole; RAV, ravuconazole; VRC, voriconazole; VRC-S, voriconazole-susceptible; VRC-R, voriconazole-resistant; IP, intraperitoneal; IV, intravenous; PO, peros (oral); q12h, every 12 h; NR, not reported; MIC, minimal inhibitory concentration.

(38.7%) recipients receiving either of the monotherapy (P=0.08; 95% CI, –21.4, 1.09). The combination therapy of voriconazole and anidulafungin results in a trend towards improved overall survivals compared with monotherapy of voriconazole in patients with proven or probable IA.

Discussion

In this review, to assess the efficacy of the combination therapy of triazole and echinocandin in treatment of IA, we systematically assessed publications on the combination therapy of triazole and echinocandin in treatment of IA, including the animal studies and clinical studies. We found that the survival in the combined therapy groups were significantly improved in the animal studies compared with monotherapy of echinocandin [RR =2.26, (95% CI, 1.79-2.78; P<0.00001)], but no statistical difference compared with monotherapy of triazole [RR =1.19, (95% CI, 0.98-1.44; P=0.08)]. It only suggests that the addition of triazole to echinocandin results in a trend towards improved overall survival in animals with IA. Meanwhile, we also found that the combination therapy of triazole and echinocandin in treating IA also results in a trend towards improved the survival in clinical studies.

To the best of our knowledge, this is the first study to assess the efficacy of the combination therapy of triazole and echinocandin in IA in both animal studies and clinical studies. However, there are some limitations in this review. First, the animal species, infective dosages of *Aspergillus*, route of infections, and antifungal drugs and doses are different

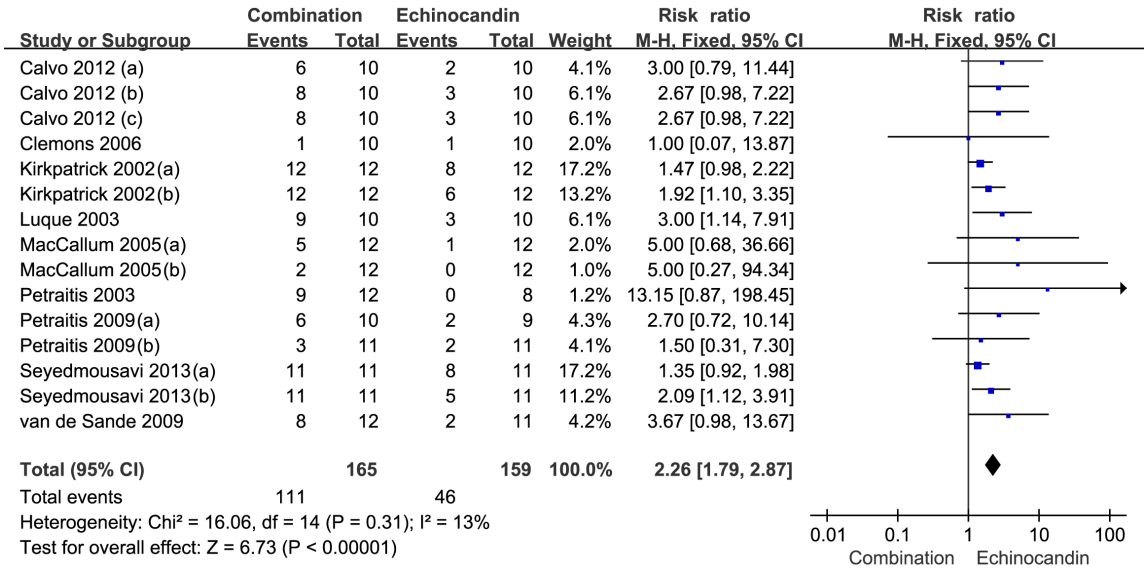

Figure 2 Forest plot showing the survival of the combination therapy of triazole and echinocandin compared with monotherapy of echinocandin in animal studies.

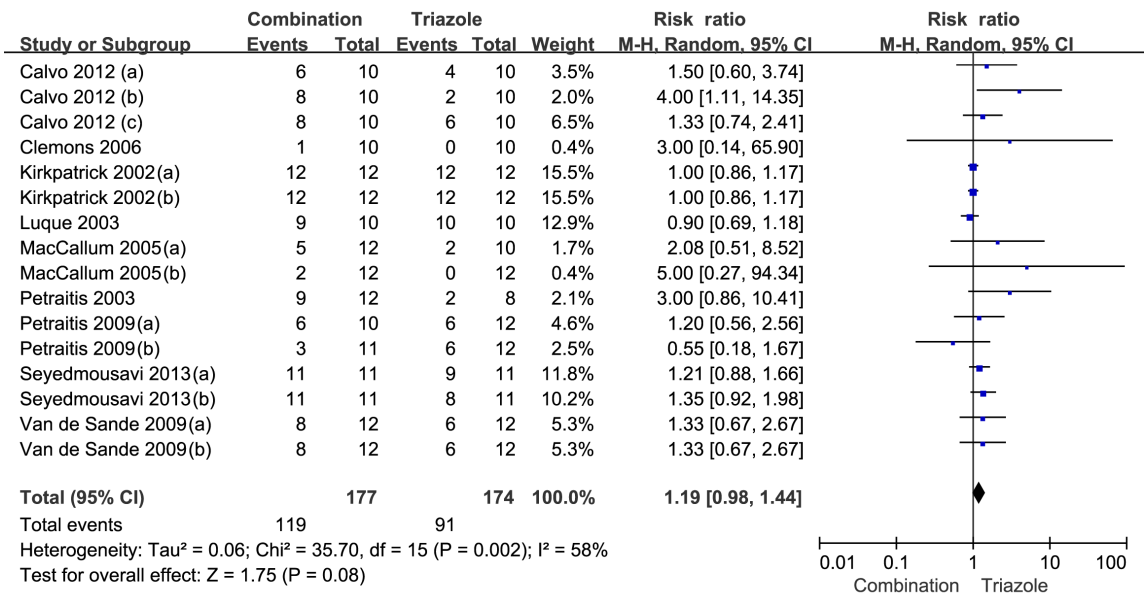

Figure 3 Forest plot showing the survival of the combination therapy of triazole and echinocandin compared with monotherapy of triazole in animal studies.

among some animal studies. Second, there may be difference between animals and humans in drug metabolism rate. For an example, the metabolic rate in rodents is faster than in humans. Third, the clinical studies contained only one RCT.

Due to the different targets of triazole and echinocandin, simultaneous inhibition of fungal cell-wall and cell-membrane biosynthesis may result in a synergistic or additive function against *Aspergillus*. However, we did not find this expected outcome in some animal studies and clinical studies. The possible causes may be ascribed to that the doses of triazole or echinocandin used in animal studies are different.

The area under the curve (AUC)/MIC ratio, a

Table 4 Characteristics of included human studies

Studies	Sample sizes	Age mean (years)	Study population	Types of studies	Treatments		Treatment duration (days)	End-point	Outcome measure
					Combination	Monotherapy			
Marr KA *et al.*, 2004 (19)	47	45	HSCT	Cohort	VRC 6 mg/kg q12h IV for 1 day and then 4 mg/kg q12h + CAS 70 mg IV for 1 day and then 50 mg/d	VRC 4 mg/kg q12h IV, AMB 1 mg/kg/day	90	Mortality	HR =0.28 (95% CI, 0.1-0.92); P=0.01
Singh N *et al.*, 2006 (20)	87	50	Organ transplant recipients	Cohort	VRC 6 mg/kg q12h IV for 1 day and then 4 mg/kg q12h + CAS 70 mg IV for 1 day and then 50 mg/d	L-AMB 5.2 mg/kg/d	90	Mortality	HR =0.58 (95% CI, 0.3-1.14); P=0.12
Upton A *et al.*, 2007 (21)	405	40.7	HSCT	Cohort	VRC + CAS	VRC (before 1996: AMB 0.5 mg/kg/day; after 1996: L-AMB 5 mg/kg/day)	90	Mortality	HR =2.3 (95% CI, 0.6-9.4); P=0.23
Rieger CT *et al.*, 2008 (22)	56	46	Haematological cancer	Cohort	VRC 6 mg/kg q12h IV for 1 day and then 4 mg/kg q12h + CAS 70 mg IV for 1 day and then 50 mg/d	L-AMB 3 mg/kg/d ± CAS 70 mg IV for 1 day and then 50 mg/d or VRC 6 mg/kg q12h IV for 1 day and then 4 mg/kg q12h	90	Efficacy; survival	No adjusted analysis
Marr KA *et al.*, 2012 (24)	277	51.9	HSCT and haematological malignancies	RCT	VRC 6 mg/kg q12h IV for 1 day and then 4 mg/kg q12h + AFG 200 mg IV for 1 day and then 100 mg/d	VRC 6 mg/kg q12h IV for 1 day and then 4 mg/kg q12h + placebo	42 or 84	Mortality	P=0.09; 95% CI, –19, 1.5 (42 days); P=0.08; 95% CI, –21.4, 1.09 (84 days)

HSCT, hematopoietic stem cell transplant; AFG, anidulafungin; AMB, amphotericin B; CAS, caspofungin; ICZ, itraconazole; L-AMB, liposomal amphotericin B; MICA, micafungin; POC, posaconazole; RAV, ravuconazole; VRC, voriconazole; IV, intravenous; IP, intraperitoneal; PO, peros (oral); q12h, every 12 h; HR, hazard ratio.

pharmacokinetic/pharmacodynamic (PK/PD) index, is used to predict triazole therapeutic efficacy (25,26) while both the AUC/MIC and the C_{max}/MIC are used to predict echinocandin therapeutic efficacy (27,28). However, according to Petraitis *et al*. (16), anidulafungin was synergistic at a dosage of 5 mg/kg/day but antagonistic at 10 mg/kg/day in the combination with voriconazole, suggesting that a higher dosage of echinocandin may be deleterious to the combination therapy. The reason for this phenomenon may be paradoxical echinocandin activity (29).

The resistance of *Aspergillus* to triazole may result in decrease of efficacy. According to a study by Seyedmousavi *et al*. (18), combination therapy of voriconazole and anidulafungin for IA was synergistic in voriconazole-susceptible *A. fumigatus*, but additive in voriconazole-resistant *A. fumigatus*.

In the RCT (24), the prolongation of survival, either six weeks (P=0.09) or 12 weeks (P=0.08), results in a trend towards improved in the combination therapy of voriconazole and anidulafungin compared with monotherapy of voriconazole. Of the four human cohort studies, two studies (19,22) observed that the combination therapy of triazole or echinocandin was associated with a significant reduction in mortality compared with other treatments and another study (20) might be a preferable therapy; However, one study (21) revealed that there was no significant difference between the combination therapy and either of the monotherapy. It suggested that the effectiveness of the combination therapy of triazole and echinocandin may be better than either of the monotherapy or other combination. Well-designed RCTs and further improved clinical trials are necessary to study the effectiveness of the combination therapy.

Acknowledgements

Funding: This work was supported by grants from the National Natural Science Foundation of China [grant number 81270064, 81200063].
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Zhang M, Sun WK, Wu T, Chen F, Xu XY, Su X, Shi Y. Efficacy of combination therapy of triazole and echinocandin in treatment of invasive aspergillosis: a systematic review of animal and human studies. J Thorac Dis 2014;6(2):99-108. doi: 10.3978/j.issn.2072-1439.2014.01.18

