Systematic Review

Single Use of Itraconazole Has No Effect on Treatment for Penicillium Marneffei with HIV Infection

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Abstract

Objective: To evaluate the efficacy of a single use of itraconazole for treating Penicillium marneffei infection in HIV-infected patients, help to develop a clinical medication regimen, and provide a scientific basis for treatment measures.

Method: A computerised literature search was carried out using the PubMed, EMbase, Ovid, Web of Science, Science Direct and CNKI (China National Knowledge Infrastructure) databases to collect relevant articles (from their establishment date to August 2014) using the following keywords: Itraconaz or Sporanox, HIV, AIDS, Penicillium marneffei (PSM), and Treatment. All related RCTs (Randomised Controlled Trials) were screened. Stata12.0 was used to conduct the meta-analysis to calculate the RR (relative risk) and 95% CI (confidence intervals). After that the consistency test, followed by the bias, was evaluated.

Results: Five RCT papers were finally enrolled, with 467 persons in total. Among them, 192 individuals were enrolled in the experimental group, of which 37 individuals (19.27%) died during the course of the study. The number of participants in the control group was 275, and of these, 55 individuals (18.55%) died over the course of the study. The meta-analysis showed that the RR and 95% CI was 1.03 and 0.69 –1.54, P > 0.05, indicating that single-use itraconazole for the treatment of Penicillium marneffei infection in HIV-infected patients was non-effective. The publication bias analysis results showed that the funnel chart was symmetrical, indicating that the effect of publication bias in this research can be ignored.

Conclusion: Single-use of itraconazole for the treatment of Penicillium marneffei infection in HIV-infected patients is non-effective.

Keywords: AIDS, HIV, itraconazole (sporanox), Penicillium marneffei (PSM), treatment

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Introduction

AIDS is still one of the heaviest burdens in the field of medicine. The number of Penicillium marneffei infections in HIV-positive patients is rising constantly. Penicillium marneffei infection is an endemic disease, particularly in Southeast Asia. Common clinical manifestations include high fever, hepatosplenomegaly, lymphadenopathy and cutaneous lesions. Penicillium marneffei was rare a few years ago. However, now it has become one of the most common AIDS-defining illnesses, especially in the northeast India, as well as across Burma (Myanmar), Cambodia, Vietnam, Taiwan and Southern China, to Indonesia. Patients are increasingly diagnosed in other parts of the world after being exposed in Asia. Therefore, it is increasingly important for those, who are working in the field of HIV to recognise this emerging infection[1] and provide a scientific basis for treatment measures.

Currently, Penicillium marneffei in HIV-infected patients is treated worldwide through the use of an antifungal comprehensive treatment. However, there are many researchers suggesting that it can be effective to use a single dose of itraconazole antifungal therapy.[2–7] There are also studies recommending the integration of Amphotericin B and itraconazole for treatment.[2,8] However, during the early development of the treatment option, itraconazole was not recommended for this purpose.[9] This leads to the question, is it actually effective to use a single dose of itraconazole as an antifungal therapy? To answer this question, in this study, clinical RCTs were used to conduct a meta-analysis, and systemically review the effectiveness of single-use itraconazole for treating Penicillium marneffei infection in HIV-infected patients.

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Materials and Methods

Document retrieval

A literature search was performed using the PubMed, EMbase, Ovid, Web of Science, Science Direct, and CNKI databases. For the search, the keywords HIV, AIDS, Penicillium marneffei (PSM), treatment, and clinical medication were used. The reference time was defined as being from the time the database was built until August 2014.

Literature inclusion criteria

Type of Study

RCTs of studies about Penicillium marneffei infection in HIV medication

Subjects

HIV-positive patients were diagnosed with Penicillium marneffei infections

Interventions

HIV and Penicillium co-infected patients received a single antifungal itraconazole (oral or topical use) daily or intermittently during treatment.

Outcomes

Penicillium infection severity was effectively controlled or mitigated, without recurrence to some extent, and lifespan was extended.

Document exclusion criteria

The original literature was excluded if their experimental design was poor, sample data were incomplete or explained unclearly, or the number of outcomes from the test and control groups could not be extracted. The repeatedly published literatures were also eliminated.

Information extraction and methodological quality of comments

Literature screening and data extraction were conducted independently by individuals. We contacted with the authors via telephone or letter if some information of their papers was unclear or missing. Jadad quality scale rating was carried out to determine studies' methodological quality, according to the following criteria (as defined by the Cochrane Handbook 5.1.0, the full scores were 5): 1) total two scores for randomized design (one score was given if just mentioned randomize design, while the other score was given if there was detailed and appropriate method description in the paper); 2) total two scores for double-blind design, one score was given if just mentioned double-blind, while the other score was given if there was detailed description of double-blind implementation in the paper; 3) total one score for introduction about the presence and loss to follow-up of participants, giving one score if there was appropriate description, otherwise 0 score. The paper with a total score of 0 to 2 was categorized into low-quality literature, while 3 to 5 was categorized into high-quality literature.

Statistical analysis

A meta-analysis was performed using Stata12.0 software. Quantitative data, using relative risk (RR) as a treatment for drug analysis, statistics, and each volume was indicated by a 95% CI value. The X^2 test was used to assess heterogeneity in the meta-analysis. A fixed effects model was applied when the data were statistically different regarding homogeneity ($P > 0.05$, $I^2 < 50\%$). Conversely, when there was heterogeneity between the data ($P < 0.05$, $I^2 > 50\%$), a random effects model was used.

Bias estimates

Sensitivity analysis was carried out by comparing the result changes between before and after excluding different weighted studies. Publication bias was determined by drawing a funnel plot, using a linear regression model (Egger France). Funnel plot's symmetry was tested, when intercept's 95% CI containing 0 ($P > 0.05$), indicating that the funnel plot was symmetrical.

Results

The basic characteristics of the study

In initial search, with merging retrospective method, we obtained 486 relevant abstracts (excluding non-RCTs), 472 of them we could not extract outcomes data from test group and control group. Through full text reading, 12 references[3–7,10–16] were remained. Then seven studies were excluded due to being incomplete or duplicate.[10–16] Ultimately, five studies met the inclusion criteria.[3–7] The process used for conducting the meta-analysis is shown in Figure 1. The basic characteristics of the included studies are shown in Table 1.

Methodological quality assessment

The results of the methodological quality evaluation are shown in Table 2. Literature included five multi-centre, randomised, blinded, and placebo control groups. Five studies,[3–7] reported a baseline of the test group and control groups, with no statistical difference between the groups, and is comparable. Four studies reported the number of exits and specific reasons for lost cases. There was a case, which was lost for unknown reasons, but the case was still included in the original statistical analysis using the method of randomisation analysis.[9] According to the Jadad score, in the included studies there were four methods that scored > 3 points, qualified these studies as high quality research.

Meta-analysis results

A total of five documents on 467 Penicillium marneffei infec-

Table 1. The basic characteristics of the included studies

Year	Literature	Author	Test group			Control group		
			Deaths(n)	Total number(N)	Mortality (%)	Deaths(n)	Total number(N)	Mortality (%)
2002	[3]	S. Chariyalertsak	12	63	19.05	11	66	16.67
1998	[4]	K. Supparatpinyo	11	36	30.56	15	35	42.86
2012	[5]	M. Larsson	11	77	14.29	5	49	10.20
2008	[6]	T. Wu	2	10	20.00	5	34	14.71
2008	[7]	L. Li	2	6	33.33	16	93	17.20

Table 2. The analysis of the quality status of the evaluation results

Literature	Randomization case	Blinded description	Lost or quit	Jadad score
[3]	Full	Only double-blind	Clear	4
[4]	Full	Only double-blind	Clear	4
[5]	Only random	Only double-blind	Clear	3
[6]	Only random	Only double-blind	Clear	3
[7]	Only random	Only double-blind	Not Clear	2

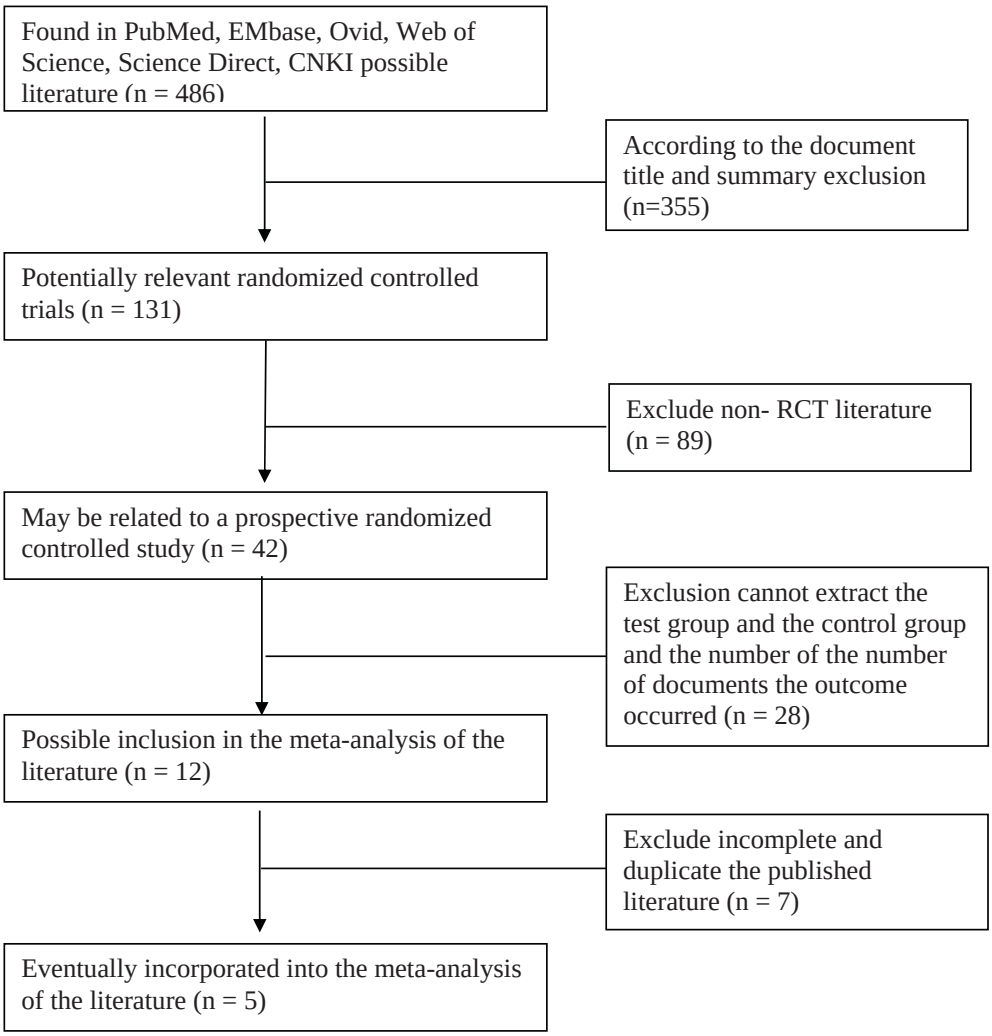

Figure 1. A literature study included in the analysis flow chart

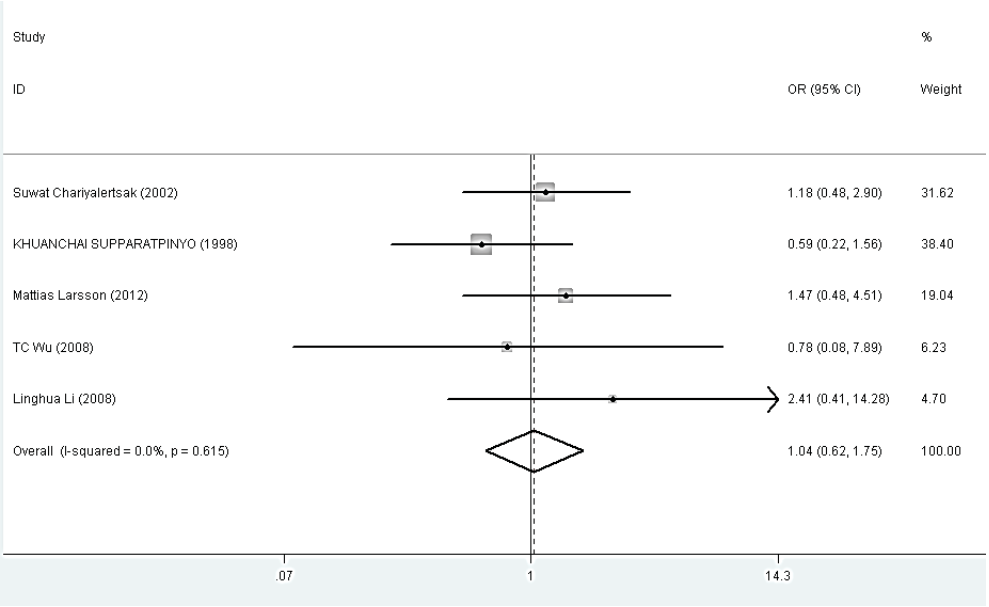

Figure 2. HIV infection Penicillium merge meta-analysis of forest plot

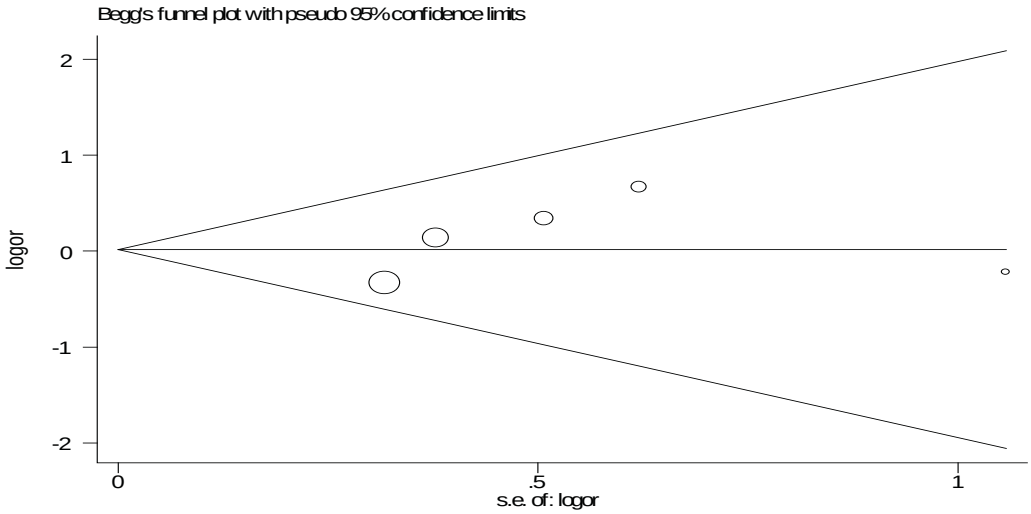

Figure 3. The analysis of included literature publication bias funnel plot

tions in HIV individuals were used, of which, the total number of the test group was 192 and the number of individuals in the control group was 275. According to the heterogeneity test (X^2 = 2.87, I^2 = 0.0%, P = 0.580), there was no heterogeneity between these studies using the fixed effect model. Considering the test group and the control group, the combined effect of the amount of RR was 1.03. This indicates that the meta-analysis was not statistically significant (95% CI: 0.69 ~ 1.54), P > 0.05, as shown in Figure 2.

Sensitivity analysis

The main characteristics that were investigated in the sensitivity analysis are: changes in inclusion criteria, exclusion of low-quality studies, use of different statistical methods and model analysis of the same information. The author removed the two samples that had low volume, weight < 10% of the literature,[4,5] or the re-estimated combined effect size RR (95% CI) value of 0.99 (0.64 ~ 1.52), P > 0.05. After switching to the random effects model, the RR (95% CI) value of 1.02 (0.68 ~ 1.52), P > 0.05, compared with the previous results of the sensitivity analysis and the results of the meta-analysis, did not change much.

Publication bias recognition

Drawing the funnel plot showed that the five included pieces of literature appeared on the map, and the combined effect of the amount of RR spreading to the distribution centre was the result of a large sample size at the top of the funnel plot (Figure 3). The linear regression analysis showed (Figure 3) the intercept of 1.031783, 95% CI value of the intercept: -2.467271 ~ 4.530837, including 0; t = 0.94, P = 0.417 > 0.05. This indicated that the funnel plot was symmetric and the research did not appear to have publication bias.

Discussion

In this study, five RCTs were enrolled in the final analysis, for a total of 467 HIV co-infection with Penicillium marneffei positive individuals, including the single-use itraconazole group (experimental group) of 192 individuals. There were 37 cases of death, making the mortality rate 19.27%. In the placebo group (control group), there were 275 individuals, with 51 cases of death and a mortality rate of 18.55%. Interventions included in the study involved the use of itraconazole. Each study used different dosing regimens and doses, while showing itraconazole being used for the treatment of HIV co-infection with Penicillium. The meta-analysis showed that HIV co-infection with Penicillium marneffei had a combined effect of the amount of RR = 1.03 (95% CI: 0.69 ~ 1.54), P > 0.05, indicating that the effectiveness of a single-use of itraconazole to treat HIV co-infection with Penicillium marneffei and the group of unused itraconazole for treatment demonstrated no differences. The publication bias analysis showed a funnel plot that was symmetrical, indicating that the impact of this research could ignore the publication bias.

Publication bias probably affects the accuracy of meta-analysis, since the studies with positive results were easier to be published, compared with the negative ones.[17] In our study, sensitivity analysis was conducted, by excluding those studies with low sample size and weight (< 10% of the literature); found that the meta-analysis results did not change much. The funnel plot analysis indicated that the various studies had a point distribution of basic symmetry that was funnel-shaped. The linear regression analysis also showed that the funnel plot was symmetrical. The funnel plot, using the Begg and Egger method, showed that the publication bias was small, indicating that the potential bias had no significant impact on the final conclusions.

These results confirm that single-use itraconazole for the treatment of HIV co-infection with Penicillium marneffe is invalid, indicating that a single-use of itraconazole could not reduce the mortality of HIV co-infection with Penicillium marneffe. Therefore, if HIV co-infection with Penicillium marneffe is experienced in clinical practice, using combination therapy should be considered rather than only using itraconazole therapy. In fact, the studies show that combining the use of penicillin B and itraconazole for the treatment of HIV co-infection with Penicillium marneffe was more feasible, demonstrating that up to 97.3% of the patients showed a significant therapeutic effect. These patients also did not have a serious adverse drug reaction.[14] Many studies jointly recommended ketoconazole with itraconazole as a treatment for mild to moderate HIV co-infection with Penicillium marneffe, making this the first drug of choice.[18]

Finally, this meta-analysis had some limitations. Future studies should be designed to be more rigorous, using more reliable methods and a multi-centre crowd RCT comprehensive analysis of the clinical research in order to make more accurate and comprehensive conclusions.

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