Title: Combination therapy of disseminated coccidioidomycosis with caspofungin and fluconazole

Authors:
Dae Won Park (pugae1@hanmail.net)
Jang Wook Sohn (jwsohn@kumc.or.kr)
Hee Jin Cheong (heejinmd@medimail.co.kr)
Woo Joo Kim (wikim@korea.ac.kr)
Min Ja Kim (macropha@chollian.net)
Je Hyeong Kim (chepraxis@korea.ac.kr)
Chol Shin (chol-shin@hanmail.net)

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Author's response to reviews: see over
Re: “Treatment of disseminated coccidioidomycosis with diffuse pneumonia by caspofungin and fluconazole”

Dear Editorial Team:

I thank the ‘BMC Infectious Diseases’ editors and referees for taking the time to review our manuscript. I have made some corrections and clarifications in the manuscript after considering the referee’s comments. The changes are summarized below.

First of all, the title of the manuscript has been changed to “Combination therapy of disseminated coccidioidomycosis with caspofungin and fluconazole” as a result of the referee’s comment, and we also believe it is more appropriate for the present case.

Referee 2 (Reviewer, Dr. Duane Hospenthal)

Major essential revisions

1. Referee’s comment: Case Presentation (page 6) - now that you have added that your patient’s CF antibody titers increased from undetectable (Day 125) to 1:256 (Day 194), you need to further describe what evaluation was done (LP? bone scan?) to rule out relapse/worsening disease. The potential implication of this should be discussed in the Discussion section as well.

Answer: Thank you for your comment.

Although our patient’s CF antibody titre increased from an undetectable level to 1:256 on day 64 after completion of the combination therapy, he had no complains, and the physical examination revealed no sign of disease progression or relapse. The CF antibody testing was carried out at the laboratory of Lynn A. Cheryk (Mayo Clinic, Minnesota, USA). Thus, we received the test results after about two months. To evaluate disease progression and relapse, we performed a chest X-ray (CXR) and computed tomography (CT) scan five months after completion of the combination
therapy. The CXR and CT revealed markedly improved findings. Also, the patient described having a sense of well-being and remains clinically healthy. He has not had any respiratory symptoms, fever, pain, headache, or weight loss. In light of the patient’s progress, we did not perform other evaluations, including a bone scan or CSF analysis. The initial bone scan and lumbar puncture revealed no abnormal findings.

This statement has been described in the Discussion section of the revised manuscript as follows:

On day 16 after initiating combined therapy with caspofungin and fluconazole, a CXR revealed a reduction in both the multiple tiny reticular nodules and the pleural effusion. The patient began to improve clinically, even though the CF antibody titre increased from an undetectable level to 1:128 after completion of combined therapy. The CF titre is considered a prognostic factor. However, our patient was clinically healthy: the skin rash had subsided, and the chest CT showed improvement. Thus, we did not perform any further evaluations. An initial bone scan and CSF analysis showed no abnormalities. The patient did not complain of a headache or localized pain (on page 9, lines 14-22).

2. Referee’s comment: Case Presentation (page 6) - a change in CF titer from 1:256 to 1:128 does not represent a decrease (4-fold change). Please remove "decreased to"

Answer: You make a good point. In accordance with your recommendation, we have removed "decreased to" on page 6, line 3 in the revised manuscript.
3. Referee’s comment: Discussion (page 7) - as this patient's titers increased from undetectable to 1:128, I would change the wording of the first sentence from "has been treated successfully" to "responded to treatment".

Answer: I agree with you. We have removed this sentence and rewritten last sentence in the Background of the revised manuscript as follows:
Here, we present the case of an immunocompetent patient with diffuse coccidioidal pneumonia who responded to caspofungin and fluconazole therapy without experiencing any adverse effects (on page 3, lines 22-24).

4. Referee’s comment: Discussion (page 9) - our report on the treatment failure with caspofungin (reference 12) did not offer proof that this failure was "because the large molecular mass, water solubility, and high protein binding of caspofungin limited penetration into the CSF". Please reword this sentence.

Answer: We have rewritten this sentence on the page 8, lines 14-18 in the revised manuscript as follows;
Furthermore, another report describes a coccidioidal meningitis treatment failure in which caspofungin was not detected in CSF, even though it was found to be above MIC in his serum [14]. We think that the limited CSF penetration of caspofungin may be due to the large molecular mass, water solubility, and high protein binding of caspofungin [10].

Minor essential revisions

5. Referee’s comment: Background (page 3) - many of the sentences are very long and poorly worded.

Answer: Thank you for your comment. We have rewritten the Background portion (on page 3) of the revised manuscript.
Discretionary Revisions

6. Referee’s comment: Title - the title could be worded better. Perhaps "Combination therapy of disseminated coccidioidomycosis with caspofungin and fluconazole"

   Answer: We appreciate your kind recommendation. In accordance with your recommendation, we have changed the title to “Combination therapy of disseminated coccidioidomycosis with caspofungin and fluconazole” in the revised manuscript.

7. Referee’s comment: Case presentation (page 4) - I would not say "suffering from various symptoms"

   Answer: Thank you for your kind advice. We have corrected first sentence in the Case presentation section of the revised manuscript.

8. Referee’s comment: Case presentation (page 5) - did the patient "complained of persistent fever" or were these documented? If fever was a sign, it should be separated from symptoms.

   Answer: Thank you for your advice. I agree with you. As recommended, we have rewritten this sentence on page 5, lines 5-8 in the revised manuscript as follows:
   However, the patient still complained of night sweats and a cough. Physical examination revealed a persistent fever (temperature of 38.6–39°C) and no improvement of the skin rash. His general condition progressively deteriorated.

9. Referee’s comment: Discussion (page 10) - I do not know of data specifically showing Korean patients any more intolerant of fluconazole. If this is because of other co-morbid conditions, hepatitis B, etc., I would suggest explaining this.
Answer: Unfortunately we have no published data on the intolerance of high-dose fluconazole in Korean patients. Therefore, this sentence has been deleted and rewritten in the revised manuscript.

I hope that our revised manuscript more precisely meets the ‘BMC Infectious Diseases’ requirements for publication. I greatly appreciate the referee’s excellent comments. Our revised manuscript was once again reviewed by native English writers for grammar and syntax.

Jang Wook Sohn, MD, PhD.
Division of Infectious Disease, Department of Internal Medicine,
Korea University, College of Medicine,
#126 Anam-dong, 5th St., Seongbuk-gu
Seoul, 136-705, Republic of Korea
E-mail: jwsohn@Kumc.or.kr, antibiotic@korea.ac.kr
Tel: +82+(2)920-5018, Fax: +82+(2)920-5616