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Caspofungin and *Pneumocystis* Pneumonia: It Is Time To Go Ahead

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We read with interest the article by Luraschi and colleagues on caspofungin and *Pneumocystis jirovecii* published in *Antimicrobial Agents and Chemotherapy* (1). Caspofungin is an echinocandin which is widely used as the first-line treatment of systemic candidiasis (2). This drug is a noncompetitive inhibitor of the subunit GSC1 of the enzymatic complex involved in 1,3-β-D-glucan synthesis, 1,3-β-glucan being a major cell wall component of most fungi. The main goal of the aforementioned study was to assess *in vitro* sensitivity of *P. jirovecii*, the human-specific *Pneumocystis* species, to caspofungin.

Nonsynonymous mutations that confer resistance to caspofungin have been identified on the *gsc1* gene of the fungal pathogen *C. albicans*. The study performed by Luraschi and colleagues concerns site-directed mutagenesis based on mutations previously identified within the *C. albicans gsc1* gene and the construction of *Saccharomyces cerevisiae* deletants for the *gsc1* gene followed by their complementation with the *gsc1* gene of wild or mutant *P. jirovecii*, *Pneumocystis murina* (the specific species in mice), and *Pneumocystis carinii* (the specific species in rats) organisms. The results showed that the drug was effective *in vitro* against *P. jirovecii*, *P. murina*, and *P. carinii* as well.

In vivo efficiency of caspofungin for treating *Pneumocystis* sp. infections has been established using rat and mouse models (3). Nonetheless, the drug essentially depletes *Pneumocystis* asci in the infected lungs, whereas it is less efficient against trophic forms (3). These results may be due to the absence or rarity of 1,3-β-D-glucan in trophic forms and the abundance of this component in ascus walls.

In this context, a potential synergistic combination based on low doses of caspofungin and co-trimoxazole and targeting asci and trophic forms has been evaluated using a mouse model. It was shown that *P. murina* could be eradicated within the lungs by this combined regimen (4). Similar combined regimens in patients with *Pneumocystis* pneumonia (PCP) have been reported (5–16) (Table 1).

In a recent study, the gene expression profiles of *P. murina* were compared between infected untreated mice and those treated with an echinocandin; results suggested that ascus formation may be necessary for *Pneumocystis* proliferation (17). These findings may explain in part the efficiency of caspofungin monotherapy in patients developing *P. jirovecii* infections, as described in four case reports (eight patients) (18–21; Table 1). Conversely, three case reports described the apparent failure of caspofungin treatment in nine patients with PCP (21, 22, 23, Table 1). Thus, efficiency of echinocandins and specifically that of caspofungin to treat *P. jirovecii* infections in humans remains a subject of controversy.

Be that as it may, original results of Luraschi and colleagues that were obtained through a fundamental approach bring strong arguments for the use of caspofungin for PCP treatment in humans. These results render it necessary to implement clinical

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TABLE 1 Main reports on *Pneumocystis* pneumonia treatment using caspofungin

Author(s) (reference), yr of publication	Patient status (no. of patients)[b]	Regimen[a]	Treatment efficacy or failure
Beltz et al. (5), 2006	ALL (1)	CAS and SMX-TMP	Efficacy
Zhang et al. (6), 2006	COPD (1)	CAS and SMX-TMP	Efficacy
Annaloro et al. (7), 2006	BMTR (1)	CAS and SMX-TMP	Efficacy
Utili et al. (8), 2007	RTR (4)	CAS and SMX-TMP	Efficacy
Mu et al. (9), 2009	CML (1)	CAS and SMX-TMP	Efficacy
Ceballos et al. (10), 2011	HIV infection (1)	CAS and SMX-TMP	Efficacy
Armstrong-James et al. (11), 2011	HIV infection (4)	CAS and SMX-TMP	Efficacy
Tu et al. (12), 2013	RTR (3)	CAS and SMX-TMP	Efficacy
Lee et al. (13), 2016	HIV (1)	CAS and SMX-TMP	Efficacy
Lu et al. (14), 2017	HTR (1)	CAS and SMX-TMP	Efficacy
Zhang et al. (15), 2018	Non-HIV immunosuppression (14)	CAS and SMX-TMP	Efficacy
Koshi et al. (16), 2019	Sjogren's syndrome (1)	CAS and SMX-TMP	Efficacy
Hof and Schnülle (18), 2008	Wegener's disease (1)	CAS	Efficacy
Lee et al. (19), 2017	HIV infection (1)	CAS[c]	Efficacy
Huang et al. (20), 2018	Autoimmune diseases (2)	CAS[c]	Efficacy
Huang et al. (21), 2019	HIV infection (7)	CAS[c]	Efficacy/failure[d]
Kamboj et al. (22), 2006	Cancer (2)	CAS	Failure
Kim et al. (23), 2013	HIV-infection (4)	CAS	Failure

[a]CAS and SMX-TMP, caspofungin and sulfamethoxazole-trimethoprim combination; CAS, caspofungin.
[b]ALL, Acute lymphoblastic leukemia; COPD, chronic obstructive pulmonary disease; RTR renal transplant recipient; CML, chronic myelomonocytic leukemia; HIV, human immunodeficiency virus; HRT, heart transplant recipient; BMTR, bone marrow transplant recipient.
[c]CAS as second-line treatment.
[d]Efficacy, 4 out of 7 cases.

trials in order to revisit the approvals by the Food and Drugs Administration in the United States or the European Medicines Agency in Europe, which did not initially consider the use of caspofungin for PCP treatment.

REFERENCES

1. Luraschi A, Richard S, Hauser PM. 2018. Site-directed mutagenesis of the 1,3-β-glucan synthase catalytic subunit of *Pneumocystis jirovecii* and susceptibility assays suggest its sensitivity to caspofungin. Antimicrob Agents Chemother 62:e01159-18. https://doi.org/10.1128/AAC.01159-18.
2. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. 2016. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 15:e1–e50. https://doi.org/10.1093/cid/civ1194.
3. Powles MA, Liberator P, Anderson J, Karkhanis Y, Dropinski JF, Bouffard FA, Balkovec JM, Fujioka H, Aikawa M, McFadden D, Schmatz D. 1998. Efficacy of MK-991 (L-743,872), a semisynthetic pneumocandin, in murine models of *Pneumocystis carinii*. Antimicrob Agents Chemother 42:1985–1989. https://doi.org/10.1128/AAC.42.8.1985.
4. Lobo ML, Esteves F, de Sousa B, Cardoso F, Cushion MT, Antunes F, Matos O. 2013. Therapeutic potential of caspofungin combined with trimethoprim-sulfamethoxazole for *Pneumocystis* pneumonia: a pilot study in mice. PLoS One 8:e70619. https://doi.org/10.1371/journal.pone.0070619.
5. Beltz K, Kramm CM, Laws HJ, Schroten H, Wessalowski R, Gobel U. 2006. Combined trimethoprim and caspofungin treatment for severe *Pneumocystis jirovecii* pneumonia in a five-year-old boy with acute lymphoblastic leukemia. Klin Padiatr 218:177–179. https://doi.org/10.1055/s-2006-933433.
6. Zhang JC, Dai JY, Fan J, Wu XP. 2006. The treatment of *Pneumocystis carinii* pneumonia with caspofungin in elderly patients: a case report and literature review. Zhonghua Jie He He Hu Xi Za Zhi 29:463–465.
7. Annaloro C, Volpe A, Usardi P, Lambertenghi Deliliers G. 2006. Caspofungin treatment of *Pneumocystis* pneumonia during conditioning for bone marrow transplantation. Eur J Clin Microbiol Infect Dis 25:52–54. https://doi.org/10.1007/s10096-005-0065-z.
8. Utili R, Durante-Mangoni E, Basilico C, Mattei A, Ragone E, Grossi P. 2007. Efficacy of caspofungin addition to trimethoprim-sulfamethoxazole treatment for severe pneumocystis pneumonia in solid organ transplant recipients. Transplantation 84:685–688. https://doi.org/10.1097/01.tp.0000280546.91617.6c.
9. Mu XD, Que CL, He B, Wang GF, Li HC. 2009. Caspofungin in salvage treatment of severe *Pneumocystis pneumonia*: case report and literature review. Chin Med J 122:996–999.
10. Ceballos ME, Ortega M, Andresen M, Wozniak A, García P, Balcells ME. 2011. Successful treatment with echinocandin in an HIV-infected individual failing first-line therapy for *Pneumocystis jirovecii* pneumonia. AIDS 25:2192–2193. https://doi.org/10.1097/QAD.0b013e32834c4c3c.
11. Armstrong-James C, Stebbing J, John L, Murungi A, Bower M, Gazzard B, Nelson M. 2011. A trial of caspofungin salvage treatment in PCP pneumonia. Thorax 66:537–538. https://doi.org/10.1136/thx.2010.135350.
12. Tu GW, Ju MJ, Xu M, Rong RM, He YZ, Xue ZG, Zhu TY, Luo Z. 2013. Combination of caspofungin and low-dose trimethoprim/sulfamethoxazole for the treatment of severe *Pneumocystis jirovecii* pneumonia in renal transplant recipients. Nephrology (Carlton) 18:736–742. https://doi.org/10.1111/nep.12133.
13. Lee WS, Hsueh PR, Hsieh TC, Chen FL, Ou TY, Jean SS. 2017. Caspofungin salvage therapy in *Pneumocystis jirovecii* pneumonia. J Microbiol Immunol Infect 50:547–548. https://doi.org/10.1016/j.jmii.2016.03.008.
14. Lu YM, Lee YT, Chang HC, Yang HS, Chang CY, Huang CM, Wei J. 2017. Combination of echinocandins and trimethoprim/sulfamethoxazole for the treatment of *Pneumocystis jiroveci* pneumonia after heart transplantation. Transplant Proc 49:1893–1898. https://doi.org/10.1016/j.transproceed.2017.04.020.
15. Zhang G, Chen M, Zhang S, Zhou H, Ji X, Cai J, Lou T, Cui W, Zhang N. 2018. Efficacy of caspofungin combined with trimethoprim/sulfamethoxazole as first-line therapy to treat non-HIV patients with severe pneumocystis pneumonia. Exp Ther Med 15:1594–1601. https://doi.org/10.3892/etm.2017.5516.
16. Koshy R, Chen T. 2019. Combination therapy with trimethoprim-sulfamethoxazole and caspofungin in a case of severe *Pneumocystis* pneumonia. ID Cases 15:e00496. https://doi.org/10.1016/j.idcr.2019.e00496.
17. Cushion MT, Ashbaugh A, Hendrix K, Linke MJ, Tisdale N, Sayson SG, Porollo A. 2018. Gene expression of *Pneumocystis murina* after treatment with anidulafungin results in strong signals for sexual reproduction, cell wall integrity, and cell cycle arrest, indicating a requirement for ascus

formation for proliferation. Antimicrob Agents Chemother 62:e02513-17. https://doi.org/10.1128/AAC.02513-17.
18. Hof H, Schnülle P. 2008. *Pneumocystis jiroveci* pneumonia in a patient with Wegener's granulomatosis treated efficiently with caspofungin. Mycoses 51:65–67. https://doi.org/10.1111/j.1439-0507.2008.01530.x.
19. Lee N, Lawrence D, Patel B, Ledot S. 2017. HIV-related *Pneumocystis jirovecii* pneumonia managed with caspofungin and veno-venous extracorporeal membrane oxygenation rescue therapy. BMJ Case Rep https://doi.org/10.1136/bcr-2017-221214.
20. Huang HB, Peng JM, Du B. 2018. Echinocandins for *Pneumocystis jirovecii* pneumonia in non-HIV patients: A case report. Exp Ther Med 16:3227–3232. https://doi.org/10.3892/etm.2018.6587.
21. Huang YS, Liu CE, Lin SP, Lee CH, Yang CJ, Lin CY, Tang HJ, Lee YC, Lin YC, Lee YT, Sun HY, Hung CC, Taiwan HIV Study Group. 2019. Echinocandins as alternative treatment for HIV-infected patients with *Pneumocystis* pneumonia. AIDS 33:1345–1351. https://doi.org/10.1097/QAD.0000000000002207.
22. Kamboj M, Weinstock D, Sepkowitz KA. 2006. Progression of *Pneumocystis jiroveci* pneumonia in patients receiving echinocandin therapy. Clin Infect Dis 43:e92–e94. https://doi.org/10.1086/508282.
23. Kim T, Hong HL, Lee YM, Sung H, Kim SH, Choi SH, Kim YS, Woo JH, Lee SO. 2013. Is caspofungin really an effective treatment for *Pneumocystis jirovecii* pneumonia in immunocompromised patients without human immunodeficiency virus infection? Experiences at a single center and a literature review. Scand J Infect Dis 45:484–488. https://doi.org/10.3109/00365548.2012.760842.