



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

^aCAS and SMX-TMP, caspofungin and sulfamethoxazole-trimethoprim combination; CAS, caspofungin.

^bALL, 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.

^cCAS as second-line treatment.

^dEfficacy, 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.

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