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Multifaceted efficacy of caspofungin against fungal infections in COVID-19 patients

ARTICLE INFO

Keywords
SARS-CoV-2
COVID-19
Caspofungin
Proinflammatory cytokine
Spleen tyrosine kinase

ABSTRACT

Fungal co-infections of coronavirus disease 2019 (COVID-19) are generally infrequent, but are more common among patients with hematological diseases or severe cases in the intensive care unit (ICU). As fungal infections often carry a high mortality rate, preventing their development is considered important for patients with COVID-19. Caspofungin covers Candida spp. and Aspergillus spp. as causative pathogens of fungal infections associated with COVID-19, and is known to have few side effects among antifungal drugs. Recent studies have shown that caspofungin is expected to inhibit the growth of severe acute respiratory syndrome coronavirus 2. In addition, the inhibitory effects of caspofungin on spleen tyrosine kinase-related intracellular signaling are anticipated to suppress the overproduction of proinflammatory cytokines and immune thrombosis, which are problems in severe COVID-19. Early use of caspofungin in patients with COVID-19 with hematological diseases or in the ICU may help prevent fungal infections and reduce severe cases in COVID-19 patients.

The rate of fungal co-infection is higher among coronavirus disease 2019 (COVID-19) patients who are critically ill or have underlying hematological diseases. The incidence of fungal co-infection in COVID-19 has been reported to range from 3.2% to 69%, with Candida spp. and Aspergillus spp. detected as the main causes of invasive fungal infections [1]. Comparing COVID-19 hematological disease patients and COVID-19 healthcare providers, fungal co-infection was significantly more common among patients with hematological disease [2]. Fungal co-infection in immunocompromised COVID-19 patients, particularly those with hematological diseases, may lead to fatal outcomes [3]. Secondary infection with COVID-19 was very frequent among patients admitted to the intensive care unit (ICU) for more than 72 h (86.6%), mostly involving respiratory infections, and the most common causative fungus was Candida albicans (6.8%) [4]. Mortality among patients with candidemia was twice as high in patients with COVID-19 (62.5%) compared to non-COVID-19 patients (32.1%) [5]. Thus, particularly in COVID-19 patients, fungal co-infections may be problematic in patients with severe forms of the disease, and early empiric interventions may be warranted. We hypothesized that empiric use of caspofungin would be helpful in both COVID-19 patients with underlying hematological disease and patients with severe COVID-19.

Caspofungin is an echinocandin antifungal agent that acts by inhibiting β-D-glucan synthase, an enzyme that does not exist in the human body. Caspofungin is known to be effective against Aspergillus spp. and Candida spp. [6].

A recent in silico analysis showed that Caspofungin targets the main protease (Mpro) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Lopinavir/ritonavir, an HIV-1 protease inhibitor, was similarly analyzed for its potential binding to Mpro in SARS-CoV-2. Caspofungin can form more hydrogen bonds with Mpro than lopinavir/ritonavir, so Caspofungin is highly resistant to SARS-CoV-2 mutation [7].

In addition, a previous study confirmed that caspofungin has the ability to inhibit the spleen tyrosine kinase (Syk)-mediated signaling pathway in host immune cells and thus suppress inflammatory cytokine and chemokine production. These results were validated in experiments with the Syk inhibitor R406, yielding similar results [8]. Syk is a non-receptor-type tyrosine kinase that is activated in innate immunity by receptors with immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic domains, such as the C-type lectin receptor dectin-1. As a result, Syk stimulates the production of inflammatory cytokines and chemokines [9–12]. Overproduction of proinflammatory cytokines is reportedly associated with severe disease in patients with COVID-19 [13] and increased production of proinflammatory cytokines has also been observed in invasive fungal infections [14].

The following findings have been reported regarding the relationship between COVID-19 and Syk inhibitors. R406 inhibits both proinflammatory cytokine release from macrophages and thrombus formation induced by anti-spike immune complexes, primarily in an FcyRIIA-dependent manner [15,16]. R406 inhibits the release of neutrophil extracellular traps (NETs) when healthy human neutrophils are stimulated in plasma from COVID-19 patients [17]. NETs have been found in the lungs of patients who died of COVID-19 and are known to promote immunothrombosis [18–20]. In addition, NETs are associated with the severity of COVID-19 [21]. R406 also inhibits mucin-1, a transmembrane protein in lung epithelium that is associated with acute respiratory distress syndrome [22].

The advantages of caspofungin can be summarized to be broad spectrum activity against fungi, including Candida spp. and Aspergillus spp., possible growth inhibition of SARS-CoV-2 itself, and inhibition of inflammatory cytokine overproduction and immunothrombosis via Syk inhibition (Fig. 1). Moreover, CAS has few side effects, relatively few drug interactions, and no need for therapeutic drug monitoring.

The timing of CAS administration is also an important consideration. Fungal infections often take time to diagnose from positive cultures, antigen tests, or other methods. Thus, agents should be given earlier to
patients at risk of the above fungal co-infections before the diagnosis is confirmed. Prompt administration of the drug is thus desirable for patients with underlying hematological diseases or severe condition who may require ICU admission, or when there are definitive image findings of pneumonia.

In COVID-19 patients, the possibility of fungal co-infections, particularly in those with severe illness or underlying hematological diseases, may be associated with poor prognosis. We suggest the addition of CAS as empiric therapy for these patients. Clinical studies are needed to validate this hypothesis.

Consent statement/Ethical approval

Not required.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Ezesokhi OT, Pohl CH. Opportunistic pathogenic fungal co-infections are prevalent in critically ill COVID-19 patients: Are they risk factors for disease severity? S Afr Med J 2020;110(11):1081-5.
[2] He W, Chen L, Chen L, Yuan G, Fang Y, Chen W, et al. COVID-19 in persons with haematological cancers. Leukemia 2020;34(6):1637-45. https://doi.org/10.1038/s41375-020-0066-7.
[3] Nasti E, Shouei P, Yakili B, Mirhendi H, Sadeghi S, Hajiaghmad S, et al. Fatal invasive pulmonary aspergillosis in COVID-19 patient with acute myeloid leukemia in Iran. Mycopathologia 2020;185(6):1077-84. https://doi.org/10.1007/s11046-020-0496-2.
[4] Sang L, Yi X, Lin Z, Pan Y, Song B, Li CA, et al. Secondary infection in severe and critical COVID-19 patients in China: a multicenter retrospective study. Ann Palliative Med 2021;10(8):8557-70. https://doi.org/10.21037/apm-21-853.
[5] Seagle EE, Jackson BR, Lockhart SR, Georgacopoulos O, Nunnally NS, Roland J, et al. The landscape of candidemia during the COVID-19 pandemic. Clin Infect Dis 2022;74(5):802-11. https://doi.org/10.1093/cid/ciaa562.
[6] Patil A, Majumdar S. Echinocandins in antifungal pharmacotherapy. J Pharm Pharmacol 2017;69(12):1635-60. https://doi.org/10.1111/jphp.12780.
[7] Liu X, Wang XJ. Potential inhibitors against 2019-nCoV coronavirus M pro tease from clinically approved medicines. J Genet Genomics 2020;47(2):119-21. https://doi.org/10.1016/j.jgg.2020.02.001.
[8] Itoh K, Shigemi H, Chihara K, Sada K, Yamauchi T, Iwasaki H. Caspofungin suppresses zymosan-induced cytokine and chemokine release in THP-1 cells: possible involvement of the spleen tyrosine kinase pathway. Transl Res 2021;227:53-63. https://doi.org/10.1016/j.trsl.2020.07.005.
[9] Fang J, Wang Y, Lv X, Shen X, Ni X, Ding K. Structure of a β-glucan from Griffola frondosa and its antimicrobial effect by activating dectin-1/Syk/NF-κB signaling. Glycoconjug J 2012;29(5-6):365-77. https://doi.org/10.1007/s10719-012-9416-z.
[10] Kimura Y, Chihara K, Honjoh C, Takeuchi K, Yamauchi S, Yoshiki H, et al. Dectin-1-mediated signaling leads to characteristic gene expressions and cytokine secretion via spleen tyrosine kinase (Syk) in rat mast cells. J Biol Chem 2014;289(45):31565-75. https://doi.org/10.1074/jbc.m114.581322.
[11] Yi YS, Son YJ, Ryon C, Sung GH, Kim JH, Cho JY. Functional roles of Syk in macrophage-mediated inflammatory responses. Mediators Inflamm 2014;2014:270302. https://doi.org/10.1155/2014/270302.
[12] Mocasai A, Ruland J, Tybuliewicz VJL. The SYK tyrosine kinase: a crucial player in diverse biological functions. Nat Rev Immunol 2010;10(6):387-402. https://doi.org/10.1038/nri2765.
[13] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):507-513. https://doi.org/10.1016/s0140-6736(20)30183-5.
[14] Prentes E, Laszing A, Mueller-UrI P, El Menzawy I, Graninger W. Cytokines in sepsis due to Candida albicans and in bacterial sepsis. Eur Cytokine Netw 1999;10(3):623-30.
[15] Hoepel W, Chen H-J, Geyer CE, Allahverdijeva S, Manz XD, de Taeye SW, et al. High titer and low faciosynostosis of early human anti-SARS-CoV-2 lgG promote inflammation by alveolar macrophages. Sci Trans Med 2021;13(596). https://doi.org/10.1126/scitranslmed.aba6654.
[16] Bye AP, Hoepel W, Mitchell JL, Jegouic S, Loureiro S, Sage T, et al. Aberrant glycosylation of anti-SARS-CoV-2 spike lgG is a prothrombotic stimulus for platelets. Blood 2021;138(16):e181-9. https://doi.org/10.1182/blood.2021011871.
[17] Strich JR, Ramos-Benitez MJ, Randazzo D, Stein SR, Babyak A, Davey RT, et al. Fostamatinib Inhibits Neutrophils Extracellular Traps Induced by COVID-19 Patient Plasma: A Potential Therapeutic. J Infect Dis 2021;223(6):961-4. https://doi.org/10.1093/infdis/jiaa789.
[18] Middleton EA, He XY, Denorme F, Campbell RA, Ng D, Salvatore SP, et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. Blood 2020;136(11):1169-79. https://doi.org/10.1182/blood.2020007008.
[19] Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol 2017;60. https://doi.org/10.1038/nri.2017.105.
[20] Veras FP, Pontelli MC, Silva CM, Toller-Kawahisa JE, de Lima M, Nascimento DC, et al. NEtS, neutrophil extracellular traps; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Syk, spleen tyrosine kinase.

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