Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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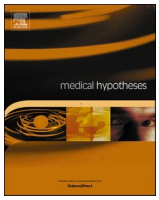

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Multifaceted efficacy of caspofungin against fungal infections in COVID-19 patients

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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 (M^{pro}) 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 M^{pro} in SARS-CoV-2. Caspofungin can form more hydrogen bonds with M^{pro} than lopinavir/ritonavir, so Caspofungin is highly resistant to SARS-CoV-2 mutation [7].

In addition, a previous study confirmed that casppofungin 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 FcγRIIA-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

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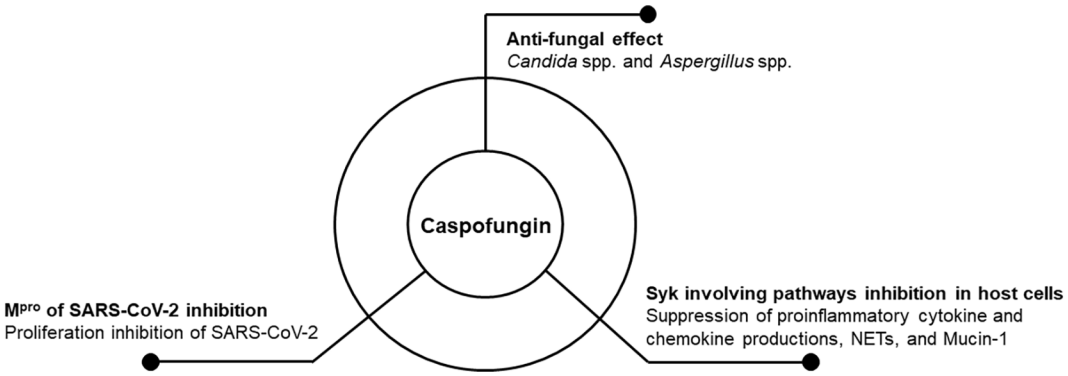

Fig. 1. Hypothesized multifaceted effects of caspofungin. M^{pro}, main protease; NETs, neutrophil extracellular traps; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Syk, spleen tyrosine kinase.

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

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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.

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