AIJR Preprints
Section: Coronavirus
Article Id: 330, Version: 1, 2021
DOI: https://doi.org/10.21467/preprints.330
URL: https://preprints.aijr.org/index.php/ap/preprint/view/330
{Click on above link or DOI to see the latest available version of this article}

NOT PEER-REVIEWED

Version 1: Received: 24 July 2021 / Approved: 14 August 2021 / Online: 22 August 2021

What Do We Know About and What Could Be the Strategy Adopted to Treat Mucormycosis on Post-COVID-19 Cases? Is It an Adjuvant Nanomaterial?

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ABSTRACT

Unfortunately, Coronavirus disease 2019 (COVID-19) remains a significant public health issue worldwide, mainly in the USA, India and Brazil. The 2nd wave of COVID-19 has reached India first. The country has been making great effort to stabilize its current condition but, unfortunately, mucormycosis infection (or black fungus) associated with COVID-19 has emerged as another threat to the country and, most likely, to Brazil. It may have happened due to excessive glucocorticoid using, since the widespread administration of this drug can lead to secondary fungal infections. Mucormycosis is generated by a group of molds called mucormycetes; it is a rare, although likely fatal, contamination when patients are not properly treated. The concerning factor lies on the fact that the high COVID-19 incidence recorded in the first wave of it has increased even faster in its second wave in India; there have been some concerning cases in Brazil, as well. The current overview addresses the current therapies used to treat mucormycosis worldwide, as well as potential and new drugs for such a specific treatment. Anti-mucormycosis adjuvants and nanomaterials are the most interesting alternatives to treat patients with post-COVID-19 mucormycosis.

Keywords: Mucormycosis, Covid-19, nanomaterials

How to Cite:

Nakazato *et al*., "What Do We Know About and What Could Be the Strategy Adopted to Treat Mucormycosis on Post-COVID-19 Cases? Is It an Adjuvant Nanomaterial?". *AIJR Preprints*, 330, Version 1, 2021.

1 Introduction

Mucormycosis (previously called zygomycosis and nowadays often called black fungus) is an extremely rare infection. It happens after contact with a group of molds called mucormycetes, which are usually found in the soil, as well as in manure, plants and in decomposing vegetables. It is also found in the nose and mucus of healthy individuals worldwide (Brunet and Rammaert, 2020). It infects individuals' sinuses, lungs and brain and poses risks to the life of severely immunocompromised patients, such as those with cancer, HIV/AIDS (Moreira et al., 2016) or COVID-19 (Singh et al., 2021).

Although mucormycosis is a rare infection that affects less than 1.7 of individuals per million population every year in the USA (e.g., San Francisco) (Kontoyiannis, 2021; CDC-2021). It is over 80 times more widespread in India, where it accounts for approximately 0.14 cases per 1000 population - and its incidence is rising (Vallabhaneni, et al., 2016). Contributory fungi are highly dependent on the environment. *Apophysomyces variabilis* is one of most prevalent fungi in Asia, whereas *Lichtheimia spp*. prevails in Europe (Dannaoui et al., 2020). Mucormycosis is the third most severe human fungal infection; it is only second to aspergillosis and candidiasis. However, it is important pointing out that mucormycosis is not contagious, i.e., it is not transmitted from person to person.

Fungal species belonging to order Mucorales are the main causative agents of mucormycosis; this order comprises more than 25 species capable of infecting humans, as reported by Dannaoui (2017). Published reports have featured 59 cases of patients with mucormycosis in Brazil and 80 cases in other South American countries (36, in Argentina; 14, in Chile; 22, in Colombia; 3, in Peru; 7, in Venezuela, 1 in Ecuador; and 1, in French Guiana); they totaled 143 cases. Rhino-sino-orbito-cerebral mucormycosis was the most frequent (approximately 10% of patients) disease type observed in Brazil, since it accounted for approximately 37% of patients (n = 22); it was followed by the pulmonary type, which accounted for 24% of patients (n = 14) in the country. Rhino-sino-orbito-cerebral sites presented high incidence of infection in 50% (n = 42) of patients living in South American countries like Brazil, whereas 33% (n = 28) of patients presented high incidence of it in soft tissues and in the skin. Mortality rate in the South American region was higher than 30% among all infection sites; except for liver and kidneys; it was higher than 60% among disseminated gastrointestinal, peritoneum and pulmonary infections (Nucci et al., 2019). Twenty-nine (29) cases of it were notified in Brazil in the last five months (https://olhardigital.com.br/en/2021/06/01/medicina-e-saude/fungo-negro-brasil-ja-tem-29-casos-da-doenca-em-2021/).

The incidence of mucormycosis in South American countries, such as Brazil, was associated with the following genera/species: *Rhizopus* spp.: *R. arrhizus* (14%) and *R. microspores* (4.2%); *Rhizomucor* spp.: *R. pusillus* (0.7%); Mucor spp.: *M. hiemalis* (1.4%) and *M. indicus* (0.7%); *Apophysomyce*s spp.: *A. elegans* (1.4%) and *A. variabilis* (0.7%); *Actinomucor elegans* (0.7%); *Lichtheimia corymbifere* (1.4%); *Cunninghamela bertholletiae* (0.7); *Syncephalastrum* spp. (0.7%); Mucorales (not otherwise specified) (50.3%) (Nucci et al., 2019).

Although India has been trying really hard to achieve stability in the current reality, the country is also fighting a form of mucormycosis, which is likely associated with the coronavirus (Singh et al., 2021). Mucormycosis is often referred to as black fungus; disease frequency rate has increased quite fast in the 2nd COVID-19 wave in comparison to the first one in India, which recorded approximately 14,872 cases by May 28th, 2021. The Indian

Council of Medical Research has shown serious concern with the need of releasing a guideline for mucormycosis analysis, diagnosis, and treatment in COVID-19 patients. Diabetes, which is a serious health issue in India, is the most common comorbidity accounting for increasing mucormycosis rates in COVID-19 patients. In addition, non-controlled corticosteroid application for immunosuppression purposes and long hospitalization time in intensive treatment units (ICU) have contributed to such an increase. It is believed that India accounted for approximately 71% of global mucormycosis cases in patients with COVID-19, based on reports from December 2019 to early April 2021 (Raut and Huy, 2021). Assumingly, the main reason for the increased rate of mucormycosis cases caused by *Rhizopus* spp. is associated with the increased prevalence of diabetes mellitus worldwide. Understanding fungal pathogenic mechanisms, such as connections between *Rhizopus* and the microenvironment found in the human body, helps developing effective antifungals to improve treatment outcomes (Morales-Franco et al., 2021).
Thus, there is global concern towards controlling these new-old diseases affecting COVID-19 patients.
The aim of the current mini-review was to assess likely new strategies or pharmaceutical materials used to treat mucormycosis.

2 Standard Therapies

Sipsas et al. (2018) conducted an interesting review of studies about mucormycosis therapies. The first-line mucormycosis therapy was associated with Amphotericin B (AMB) and with its lipid derivatives. Isavuconazole has been also investigated (Marty et al., 2016), besides these formulations - Posaconazole was only used as rescue treatment in one case (Tissot et al., 2017). The effectiveness of these drugs was associated with scarce clinical data and with preclinical data *in vitro/in vivo*, which have evidenced their activity against Mucorales. It is worth emphasizing that breakpoint MIC (minimum inhibitory concentration) validity was not tested for any of these drugs (Caramalho et al., 2015; Tissot et al., 2017).
Lipid nanocarriers, such as liposomal amphotericin B (AMB) LAMB and amphotericin B lipid complex (ABLC), have shown therapeutic index effectiveness higher than that of amphotericin B deoxycholate. They are acknowledged as the gold-standard therapy for mucormycosis (Shoham et al., 2010; Tissot et al., 2017).
Triazoles are also used to treat mucormycosis, since they are capable of consuming ergosterol in fungal cell membrane. However, most of them are ineffective against Mucorales, such as the case of itraconazole, fluconazole and voriconazole. However, new triazoles, known as Isavuconazole and Posaconazole, have shown high activity *in vitro* against Mucorales in some clinical trials that have encouraged their application in mucormycosis cases (Nagappan et al., 2007; Marty et al., 2016;).

3 Adjuvant Therapy

Poor marrow function recovery or long-term treatment with immunosuppressive drugs are the main causes of death among mucormycosis patients. Thus, hematopoietic growth factors or leukocyte transfusion are alternative protocols to help reversing neutropenia in hematological patients. This process should be gradually reduced in some immunosuppression treatments based on corticosteroid application in patients with autoimmune diseases. Furthermore, non-steroidal therapies should be changed, whenever possible (Sipsas et al., 2018).

Extra previous treatment with anti-retroviral therapy should be taken into consideration in cases of patients with HIV/AIDS in order to help strengthening their immune system before mucormycosis therapy application. Exhaustive glycemic control is extremely important for patients with acute diabetes and ketoacidosis. It is possible partly blocking endothelial cell invasion by *Rhizopus oryzae* through sodium bicarbonate application, as well as repairing individual iron chelation and neutrophil role (Gebremariam et al., 2016) through siderophores (such as deferasirox) using (Ibrahim et al., 2007). However, the risk of associating this treatment with patients affected by hematologic malignancies is quite high, based on report of increased death rate due to liposome amphotericin B application in association with deferasirox (Spellberg et al., 2012). However, different treatments can be applied to high-risk patients, such as diabetic individuals affected by hematologic diseases and mucormycosis (Cornely et al., 2014). Most specifically, patients with low-pH ketoacidosis present increased unbound iron contents in their tissues, a fact that leads to Mucorales development. Hyperbaric oxygen therapy has improved neutrophils' action and contributed to amphotericin B activity by reducing acidosis (Tragiannidis and Groll, 2009). Besides, oxygen pressure suppressed fungal development and enhanced wound healing; thus, it can be used as auxiliary therapy to surgical and antifungal treatments applied to this fungal infection (e.g.diabetic patients with sinusitis or skin infection caused by mucormycosis) (Barratt et al., 2001; John et al., 2005). Hyperbaric oxygen using as adjuvant therapy was extremely beneficial to diabetic patients, although it did not help patients with hematological diseases or especial bone marrow transplant cases (John et al., 2005). However, lack of feasible studies and controls makes the effectiveness of this procedure at least controversial (Sipsas et al., 2018). Immune enhancement (e.g., application of granulocyte (macrophage) colony-stimulating factor, interferon-γ) is one of the strategies suggested as adjuvant treatment for mucormycosis (Gil-Lamaignere et al., 2005). Granulocyte transfusions did not show clear effectiveness and posed some risk to patients with inflammatory lung injury (Hubel, et al. 2001). Statins presented antifungal action *in vitro* and *in vivo* against *Rhizopus* spp. (Bellanger et al., 2016). They are immunomodulators applied in certain COVID-19 cases (Durán and Fávaro, 2020a). An immunosuppressed patient with unmanageable mucormycosis was treated with the combination of interferon-gamma and nivolumab, and it presented excellent outcome (Grimaldi et al., 2017). Nivolumab is a monoclonal antibody capable of reducing PD-1 (programmed death-1) expression in T-cells and interferon-gamma (IFN-γ); it recovered monocyte activity and was considered a safe treatment for fungal infections (Gamaletsou et al., 2014). Anti-PD-1 was applied to murine models and was highly effective against fungal sepsis (Attanasio and Wherry, 2016).

Systematic review conducted by Garg et al (2021) addressed several mucormycosis cases. Two subjects presented symptoms suggesting mucormycosis (rhino-orbital mucormycosis), whereas others developed mucormycosis after the COVID-19 treatment (often after 10- to 14-day hospitalization) (Werthman-Ehrenreich, 2020; Mekonnen et al., 2021). Remdesivir and tocilizumab were also used with caution in some patients treated with glucocorticoids (Garg et al., 2021).

A COVID-19 patient presented an interesting case. The onset of COVID-19 symptoms in a 66-year-old patient was reported one week before he was hospitalized. He was treated with hydroxychloroquine and lopinavir-ritonavir for 10 days. Since his condition got worse, and his C-reactive protein and procalcitonin levels were high, he was subjected to experimental antibiotic treatment (levofloxacin and piperacillin-tazobactam administered through IV

infusion). At this time, he was diagnosed with mucormycosis. Forty (40) days after he was hospitalized in the ICU, and 20 days after the beginning of liposomal Amphotericin B treatment, *Rhizopus* spp. growth could still be detected in bronchoalveolar lavage analysis; the patient presented clinical improvement and recovered from lymphopenia. Since the infection persisted, the liposomal amphotericin B treatment was discontinued and a new therapy based on isavuconazole was implemented. However, his clinical condition got worse again in the following week; he presented fever, increased procalcitonin, acute hemodynamic instability and deteriorated kidney and liver functions, which were likely caused by bacterial coinfection. Unfortunately, despite the association between antifungal treatment with isavuconazole and antibiotic treatment, the patient died due to recalcitrant shock and liver malfunction, 1 month after hospitalization in the ICU (Pasero et al., 2020).

4 Nanomaterials Acting on Mucormycosis

Nanotechnology has been applied to fungal infections since the 1990´s and some mucormycosis cases have been reported since then (Voltan et al., 2016; Brunet and Rammaert, 2020), mainly in patients treated with amphotericin B colloidal dispersions (Tkatch et al., 1993; Moses et al., 1998; Vidovic et al., 2013; Herbrecht et al., 2001), amphotericin B lipid complex (Hunstad et al., 1999) and liposome amphotericin B (Fisher et al., 1991; Munckhof et al., 1993; Lim, et al., 1994; Ogawa et al., 2012).

As previously mentioned, there are other nanostructured drugs, besides these amphotericin B derivatives. Biogenic silver nanoparticles (AgNPs) were used against different bacteria and species belonging to genus *Mucor* sp. (ATCC n. 48559). Results have shown that this material might be applicable to pharmaceutic products, drug delivery systems, biosensors and antifungal drugs (Kathiravan et al., 2015).

Biogenic synthesis of AgNPs through *Aloe vera* extracts presented the highest antifungal properties against *Rhizopus sp*., as confirmed in MIC (minimum inhibitory concentration) value of 21.8 ng/mL, in comparison to pure plant extracts (applied alone), which did not record any inhibition value (Medda, et al., 2015).

Rao and Savitramma (2011) have investigated biogenic AgNPs deriving from *Svensonia hyderabadensis* leaf extract and found significant inhibition zone against *Rhizopus arrhizus*. *S*imilarly, AgNPs deriving from *Pongamia glabra* dry leaf aqueous extract used against *Rhizopus nigricans* have shown that approximately 20 µM of AgNPs was capable of substantially and effectively repressing *R. nigricans* mycelia weight, and of diminishing spore count, in comparison to crude extract of *P. glabra* (Sahayaraj et al., 2020).

According to Gunalan et al. (2012), ZnO nanoparticles presented promising antifungal activity against *Rhizopus stolonifera*. A study has shown the effectiveness of different MgO, and ZnO nanoparticle concentrations on spore germination of fungal species such as *Rhizopus stolonifer* and *Mucor plumbeus* (Wani and Shah, 2012).

Ten (10) clinical isolates from several Mucorales species were investigated. Total MIC of 1:64 in *Rhizopus delemar;* 1:4, in *R. microsporus;* 1:32, in *Mucor circinelloides;* 1:32, in *Cunninghamella;* and 1:4, in *Lithemia* were observed 1 hour after incubation with NB-201 nanoemulsion (emulsification comprising pure soybean oil, glycerol, Tween 20, EDTA, water and surfactant benzalkonium chloride). In addition, lower MIC values were recorded after longer incubation periods (Garcia et al., 2019ab).

Biosergen has funded the clinical development of BSG005. Assumingly, this compound is a potentially disruptive antifungal drug with blockbuster potential, safety and likely advantages

over competing antifungals (e.g., Amphotericin B, Nystatin). The research focused on fungal infections capable of killing hundreds of thousands of immune-compromised (AIDS), cancer and transplanted patients on a yearly basis. BSG005 was highly effective against relevant fungal strains in comparison to current treatment standards. In addition, it did not show kidney toxicity, similar to commercial drugs with great potential to treat mucormycosis. The Company is also developing BSG005 *Nano;* this drug is packed in special nanoparticles to specifically target patients' lungs, which are often the first organs affected by invasive fungal infections. Nowadays, Biosergen has required orphan drug status for BSG005 - it is expected to file the NDA by the end of 2025 (Andersen, 2021).

A new nanostructured immunomodulator from NIMM-Pharma (Brazilian startup), called OncoTherad, also appeared to be effective against COVID-19. Based on the mechanistic knowledge about OncoTherad immunotherapy, and after having investigated the function of, and role played by, interferon signaling pathway in COVID-19 contamination cases at University of Campinas (Brazil) for 15 years, it was possible featuring the potential activity of this immunotherapy to manage COVID-19 infection in several non-muscle invasive bladder cancer (NMIBC) patients (CAAE: 93619718.7.0000.5404; Brazilian Clinical Trial RBR-6swqd2), who tested positive for COVID-19 (Fávaro et al., 2019; Alonso et al., 2020; Durán and Fávaro, 2020b; Alonso et al., 2021). None of the investigated patients was intubated and their hospitalization time has shortened from approximately 11 to 5 days.

5 Final Remarks

Old drugs, such as amphotericin B, its lipid derivatives and isavuconazole, have been investigated as gold standard therapy or as first-line treatment for mucormycosis, despite several issues associated with their toxicity level and production cost. Another drug, called Posaconazole, has been used as rescue treatment. The effectiveness of the aforementioned drugs is substantiated by limited preclinical or clinical data, which evidenced activity against Mucorales.

In terms of adjuvant procedures, it was possible partly blocking endothelial cell invasion by *Rhizopus* spp. based on palliative treatments such as sodium bicarbonate, which enabled repairing host iron chelation and neutrophil functions associated with siderophores. Unfortunately, this treatment has posed significant risk to patients affected by hematologic malignancies. Interestingly, hyperbaric oxygen treatment enhanced neutrophils' functionality and contributed to amphotericin B's action by reversing acidosis. Immune enhancement strategies have been suggested as adjuvant treatment. Unfortunately, granulocyte transfusion success was not clear and presented risk of inflammatory lung damage.

Immunosuppressed patient with unmanageable mucormycosis was subjected to interferon-gamma/nivolumab association and presented excellent outcome. Therapy based on remdesivir and tocilizumab was effectively applied under similar conditions.

Nanomaterials, such as Ag, ZnO and MnO nanoparticles and nanoemulsions, besides liposomes, appeared to be effective against *Rhizopus* sp. and *Mucor* sp.

Two new drugs - BSG005 *Nano* and nanostructured Oncotherad - emerged as relevant adjuvant treatments for mucormycosis.

Thus, based on the proper mucormycosis diagnosis, it is possible adopting a promising set of conventional and new drugs to treat the disease; however, the challenge faced by health professionals lies on applying some of them at clinical stage.

6 Acknowledgements

The authors would like to thank the Sao Paulo Research Council (FAPESP grant 2018/10052-1), the Brazilian National Council for Scientific and Technological Development (CNPq grant 552120/2011-1) and Coordinating Agency for Advanced Training of Graduate Personnel (CAPES – funding code: 001).

7 Conflict-of-interest

The authors have no conflicts of interest to declare.

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