Reviewing the Effects of Miltefosine and Suggesting It for the Treatment of Coronavirus Disease (COVID-19)

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ABSTRACT

OBJECTIVE: Miltefosine is an anti-cancer drug used to treat leishmaniasis and deadly opportunistic free-living amoeba and other deadly pathogenic microorganisms. Several studies have demonstrated its antiviral effect. In this study, we discuss the effectiveness of this drug on pathogenic microorganisms, and according to the functional system of the medicine, we present this drug as a therapeutic proposal to treat Coronavirus disease (COVID-19).

METHODS: A literature search was conducted in electronic databases, including Pubmed, Science Direct, Elsevier, and Google Scholar, and articles published from 2006 to 2020 (the last decade) were selected. The search keywords included Miltefosine, microorganism, pathogen, and treatment.

RESULTS: The studies indicated that Miltefosine had therapeutic effects on leishmaniasis and deadly opportunistic free-living amoeba and other deadly pathogenic microorganisms. Several studies have proven its antiviral effect.

CONCLUSION: Owing to the beneficial effects of this drug on pathogenic and deadly microorganisms and antiviral effects, and due to the epidemic of Coronavirus and the lack of effective treatment and vaccine, this drug is recommended as one of the treatment options for this disease.

KEYWORDS: Miltefosine, COVID-19, treatment

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Introduction

Coronavirus disease 2019 (COVID-19), known as the acute respiratory infection causing respiratory tract infections, is an infectious disease caused by a coronavirus. Coronaviruses constitute the subfamily Orthocoronavirinae in the family Coronaviridae. In December 2019, it began from China, causing pneumonia outbreaks first in the Wuhan region and then in all parts of the world. It has spread across the world affecting nearly 21 million people with a toll of 0.75 million deaths and restricting the movement of most of the world population during the past 6 months. COVID-19 became the leading health, economic, and humanitarian challenge of the twenty-first century. Currently, no vaccines or antiviral drugs exist to prevent or treat COVID-19 infections. Miltefosine is an anti-cancer drug used to treat leishmaniasis and deadly opportunistic free-living amoeba and other deadly pathogenic microorganisms. Several studies have demonstrated its antiviral effect. In this study, we discuss the effectiveness of this drug on pathogenic microorganisms, and according to the functional system of the medicine, we present this drug as a therapeutic proposal to treat Coronavirus disease (COVID-19).

Methods

A literature search was conducted in electronic databases, including Pubmed, Science Direct, Elsevier, and Google Scholar, and articles published from 2006 to 2020 (the last decade) were selected. The search keywords included Miltefosine, microorganism, pathogen, and treatment.

Results and Discussion

Favipiravir is currently considered an effective drug to treat this disease. Favipiravir is new compared to existing influenza antivirals that mostly prevent entry and exit of the virus from cells. The active Favipiravir-RTP selectively prevents RNA polymerase and avoids replication of the viral genome. The increased pH in endosomes prevents virus particles from utilizing their activity for fusion and entry into the cell. Favipiravir has a similar mechanism to remdesivir but is orally administered. The initial results from the first Indian study with this drug have been hopeful with small but significant improvement in time to clinical recovery and a 2-day shorter viral shedding time. The main advantages of favipiravir are that it is administered orally and that it can be given in patients who are symptomatic but not ill enough to be hospitalized. As most COVID-19 patients (85%) have mild to moderate illness and can be treated at home, this drug could potentially be used in large numbers of patients. Thus, favipiravir may emerge as a valuable drug in the treatment of mild to moderate symptomatic SARS CoV-2 infected cases. Another effective drug is chloroquine. Chloroquine passively diffuses through cell membranes and into endosomes, lysosomes,
Cryptococcus neoformans, associated with induction of type-I interferon (IFN) in human cells.\textsuperscript{25} which is due to quick secretion of soluble features and is associ-
ated with inducing type-I IFN in human cells.\textsuperscript{25} This mechanism is likely to be a common feature of viral infections, where the virus uses type-I IFN as a way to evade the immune system.\textsuperscript{25}

SARS-CoV-2 spike protein, leading to further inhibition of viral entry.\textsuperscript{8} SARS-CoV-2 spike protein may less efficiently relate with the SARS-CoV-2 target for cell pass. ACE2 that is not in the glyco-
sylated state may less efficiently relate with the SARS-CoV-2 spike protein, leading to further inhibition of viral entry.\textsuperscript{8}

Miltefosine is used in the treatment of infections resistant to current drugs.\textsuperscript{19} Animal studies reveal that Miltefosine may be effective against Chagas' disease.\textsuperscript{19} It is effective against typhoid fever, typhoid fever, and vibrio cholerae.\textsuperscript{20} An in study found that Miltefosine was effective compared to met-
ronidazole-resistant variants of Trichomonas vaginalis.\textsuperscript{21} Cetrimonium bromide, a compound related to Miltefosine, was con-
firmed to have in vitro activity against Plasmodium falcipa-
rum.\textsuperscript{22} However, regarding the function of this drug in viral dis-
ases, it is reported that Miltefosine targets HIV infected macrophages playing a role in vivo as long-lived HIV-1 reservoirs. The HIV protein Tat activates the pro-survival PI3K/Akt pathway in primary human macrophages. Miltefosine performance by stopping the PI3K/Akt way, therefore removing the infected macrophages from circulation without affecting healthy cells.\textsuperscript{23,24} It suggestively decreases the reproduction of HIV-1 in cocultures of human dendritic cells (DCs) and CD4+ T cells, which is due to quick secretion of soluble features and is associ-
ated with induction of type-I interferon (IFN) in human cells.\textsuperscript{25}

Concerning the effects of this drug on the treatment of chikun-
gunya virus (CHIKV) viral infection, it was shown that inhibition of Akt-phosphorylation significantly inhibited CHIKV replication. No result on CHIKV replication was detected after treatment with PI3-kinase and mTOR activation inhibitors. Also, Miltefosine, an FDA-approved Akt-inhibitor, inhibited CHIKV replication in pre- and post-infection treatment. Akt-
phosphorylation can be an amenable target of therapy against CHIKV infection.\textsuperscript{26} Contrasting other DNA-targeting anticancer factors, APL drugs are involved in phospholipid metabolism, non-vesicular cholesterol transport and homeostasis, biochemical survival pathways for example, Akt-mTOR pathway, and interplay with membrane signal transduction proteins, such as phospholipase C, phospholipase D, and protein kinase C. But the exact mechanism has not been entirely elucidated yet.\textsuperscript{27}

Miltefosine presents potent antitumor activity in vitro and in experimental animal models. Nevertheless, clinical use is limited due to side effects associated with its amphiphilic nature.\textsuperscript{28-30} Uznova and et al showed Miltefosine affect the synthesis of choline-containing phospholipids, including sphingomyelin, they reported for the first time that it also reduces S1P. they sug-
gested a putative mechanism underlying the effect of miltefosine on sphingosine kinase 1, involving miltefosine-induced inhibi-
tion of protein kinase C. their findings provide a possibility for treatment of lung cancer cells.\textsuperscript{31} To date, established that S1P regulates various physiological and pathological processes such as proliferation, migration, carcinogenesis, inflammation and an giogenesis, among others.\textsuperscript{32} The family of alkylphosphocholines (APC) represents a group of antitumor agents, exhibiting a high selectivity toward tumor cells.\textsuperscript{33,34} Several drugs being re-consider-
ed for COVID-19 therapy are or have been used in cancer therapy. Indeed, virus infected cells are pushed to enhance the synthesis of nucleic acids, protein and lipid synthesis and boost their energy metabolism, in order to comply to the "viral pro-
gram." Indeed, the same features are seen in cancer cells, making it likely that drugs interfering with specific cancer cell pathways may be effective as well in defeating viral replication.\textsuperscript{35} The for-
cedly limited number of drugs appear to act essentially through selected mechanisms, that is, (a) inhibition of the PI3K/AKT to SGK1/mTOR signaling cascade; (b) inhibition of the cytokine storm; and (c) inhibition of viral nucleic acid synthesis. The activation of the PI3K/AKT to SGK1/mTOR pathway appears fundamental for supporting the replication of various virus species in the host.\textsuperscript{36-39} Based on our experience of Miltefosine usage in the treatment of infectious diseases, we recommend fur-
ther investigation of the antiviral effect of this molecule on SARS-CoV-2 and suggest Miltefosine as another potential drug to treat COVID-19 disease. We hope that these findings may pave the way for a more comprehensive clinical experimentation on repurposing of “old” drugs to the treatment of COVID-19.

Conclusion
Owing to the beneficial effects of this drug on pathogenic and deadly microorganisms and antiviral effects, and due to the epidemic of Coronavirus and the lack of an effective treatment and vaccine, this drug is recommended as one of the treatment options for this disease.

Author Contributions
In this article, the author has collected information based on scientific databases and written the article.
