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

Alireza Latifi

School of Public Health, Department of Medical Parasitology and Mycology, Tehran University of Medical Sciences, Tehran, Iran

Infectious Diseases: Research and Treatment
Volume 13: 1–3

DOI: 10.1177/1178633720977488
SAGE

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

RECEIVED: April 23, 2020. **ACCEPTED:** November 3, 2020.

TYPE: Review

FUNDING: The author received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Alireza Latifi, School of Public Health, Department of Medical Parasitology and Mycology, Tehran University of Medical Sciences, Tehran, Iran.
Email: arlatifi@yahoo.com

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.[1] In December 2019, it began from China, causing pneumonia outbreaks first in the Wuhan region and then in all parts of the world.[2,3] 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.[4] 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.[5] The increased pH in endosomes prevents virus particles from utilizing their activity for fusion and entry into the cell.[6-8] 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.[9] Another effective drug is chloroquine. Chloroquine passively diffuses through cell membranes and into endosomes, lysosomes,

and Golgi vesicles, where it becomes protonated, resulting in trapping the chloroquine in the organelle and raising the surrounding pH.10, 13. However, Hydroxychloroquine increase in human organelles raises their pH, thereby inhibiting antigen processing, preventing the alpha and beta chains of the major histocompatibility complex (MHC) class II from dimerizing, inhibiting antigen presentation of the cell, and reducing the inflammatory response.[10] Hydroxychloroquine prevents terminal glycosylation of ACE2, the receptor that SARS-CoV and SARS-CoV-2 target for cell pass. ACE2 that is not in the glycosylated state may less efficiently relate with the SARS-CoV-2 spike protein, leading to further inhibition of viral entry.[8] Miltefosine is a medication mainly used to treat leishmaniasis and against deadly protozoan Pathogens such as *Naegleria fowleri* and *Balamuthia mandrillaris*. Miltefosine was first made in the early 1980s and studied as a treatment for cancer.[11] Miltefosine on the World Health Organization's List of Important Medications, the safest and most effective drugs required in a health system.[12] Miltefosine performs its activity by interacting with lipids, inhibiting cytochrome c oxidase and causing apoptosis-like cell death.[13] Miltefosine was structurally only between lipids having an anticancer property in that it absences the glycerol group, is very selective on cell types, and acts through different mechanisms.[14,15] It is active against some bacteria and fungi as well as human trematode *Schistosoma mansoni.*[16-18] Miltefosine is under study by researchers interested in finding handlings for infections resistant to current drugs. Animal studies reveal that Miltefosine may be effective against Chagas' disease.[19] It is effective against types of fungus: *Cryptococcus neoformans*, *Candida*, *Aspergillus* and, *Fusarium.*[20] An in study found that Miltefosine was effective compared to metronidazole-resistant variants of *Trichomonas vaginalis.*[21] Cetrimonium bromide, a compound related to Miltefosine, was confirmed to have in vitro activity against *Plasmodium falciparum.*[22] However, regarding the function of this drug in viral diseases, 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 performances by stopping the PI3K/Akt way, therefore removing the infected macrophages from circulation without affecting healthy cells.[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 associated with induction of type-I interferon (IFN) in human cells.[25] Concerning the effects of this drug on the treatment of *chikungunya* 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.[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.[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.[28-30] Uzunova 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 suggested a putative mechanism underlying the effect of miltefosine on sphingosine kinase 1, involving miltefosine-induced inhibition of protein kinase C. their findings provide a possibility for treatment of lung cancer cells.[31] To date, established that S1P regulates various physiological and pathological processes such as proliferation, migration, carcinogenesis, inflammation and an giogenesis, among others.[32] The family of alkylphosphocholines (APC) represents a group of antitumor agents, exhibiting a high selectivity toward tumor cells.[33,34] Several drugs being re-considered 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 program." 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.[35] The forcedly 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.[36-39] Based on our experience of Miltefosine usage in the treatment of infectious diseases, we recommend further 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.

Ethics Approval and Consent to Participate

Ethics approval was not required for this study.

ORCID iD

Alireza Latifi https://orcid.org/0000-0002-7118-1756

REFERENCES

1. de Groot RJ, Baker SC, Baric R, et al. Family coronaviridae. In: King AM, Lefkowitz E, Adams MJ, et al, eds. *International Committee on Taxonomy of Viruses, International Union of Microbiological Societies. Virology Division. Ninth Report of the International Committee on Taxonomy of Viruses*. Elsevier; 2011: 806-828. ISBN 978-0-12-384684-6.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-733. doi:10.1056/NEJMoa2001017
3. Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. *Int J Antimicrob Agents*. 2020;55:105924. doi:10.1016/j.ijantimicag.2020.105924
4. Tazerji SS, Duarte PM, Rahimi P, et al. Transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to animals: an updated review. *J Transl Med*. 2020;18:1-1.
5. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proc JPN Acad Ser B Phys Biol Sci*. 2017;93:449-463. doi:10.2183/pjab.93.027
6. Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine. Focus on recent advancements. *Clin Pharmacokinet*. 1996;31:257-274. doi:10.2165/00003088-199631040-00003
7. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:269-271. doi: 10.1038/s41422-020-0282-0. Epub 2020 February 4.
8. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. doi:10.1186/1743-422X-2-69
9. Agrawal U, Raju R, Udwadia ZF. Favipiravir: a new and emerging antiviral option in COVID-19. *Med J Armed Forces India*. Published online September 2, 2020.
10. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rheum*. 1993;23:82-91.
11. American Society of Health-System Pharmacists (26 February 2016). Miltefosine monograph for professionals. https://www.drugs.com/monograph/miltefosine.html. *www.drugs.com*. Accessed November 16, 2016. Archived https://web.archive.org/web/20161117145201/https://www.drugs.com/monograph/miltefosine.html) from the original on 17 November 2016.
12. World Health Organization. *World Health Organization model list of essential medicines: 21st list 2019*. World Health Organization.hdl:10665/325771. 2019. https://hdl.handle.net/10665%2F325771.WHO/MVP/EMP/IAU/2019.06. License: CC BY-NC-SA 3.0IGO.
13. FDA. Miltefosine (Impravido) for the treatment of Visceral, Mucosal and Cutaneous Leishmaniasis. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM371074.pdf) (PDF). Archived (https://web.archive.org/web/20161024125444/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiInfectiveDrugsAdvisoryCommittee/UCM3710
14. Eibl H, Unger C. Hexadecylphosphocholine: a new and selective antitumor drug. *Cancer Treat Rev*. 1990;17:233-242.
15. Hilgard P, Stekar J, Voegeli R, et al. Characterization of the antitumor activity of hexadecylphosphocholine (D 18506). *Eur J Cancer Clin Oncol*. 1988;24:1457-1461.
16. Dorlo TP, Balasegaram M, Beijnen JH, de Vries PJ. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. *J Antimicrob Chemother*. 2012;67:2576-2597. doi:10.1093/jac/dks275
17. Pachioni Jde A, Magalhães JG, Lima EJ, et al. Alkylphospholipids—a promising class of chemotherapeutic agents with a broad pharmacological spectrum. *J Pharm Pharm Sci*. 2013;16:742-759.
18. Eissa MM, El Bardicy S, Tadros M. Bioactivity of miltefosine against aquatic stages of Schistosoma mansoni, Schistosoma haematobium and their snail hosts, supported by scanning electron microscopy. *Parasit Vectors*. 2011;4:73. doi:10.1186/1756-3305-4-73
19. Saraiva VB, Gibaldi D, Previato JO, et al. Proinflammatory and cytotoxic effects of hexadecylphosphocholine (miltefosine) against drug-resistant strains of Trypanosoma cruzi. *Antimicrob Agents Chemother*. 2002;46:3472-3477.
20. Widmer F, Wright LC, Obando D, et al. Hexadecylphosphocholine (miltefosine) has broad-spectrum fungicidal activity and is efficacious in a mouse model of cryptococcosis. *Antimicrob Agents Chemother*. 2006;50:414-421.
21. Blaha C, Duchêne M, Aspöck H, et al. In vitro activity of hexadecylphosphocholine (miltefosine) against metronidazole-resistant and –susceptible strains of Trichomonas vaginalis. *J Antimicrob Chemother*. 2006;57:273-278.
22. Choubey V1, Maity P, Guha M, et al. Inhibition of Plasmodium falciparum choline kinase by hexadecyltrimethylammonium bromide: a possible antimalarial mechanism. *Antimicrob Agents Chemother*. 2007;51:696-706. Epub 2006 December 4.
23. Chugh P, Bradel-Tretheway B, Monteiro-Filho CM, et al. Akt inhibitors as an HIV-1 infected macrophage-specific anti-viral therapy. *Retrovirology*. 2008;5:11. doi:10.1186/1742-4690-5-11
24. Parasitic Drug Shows HIV-Fighting Promise. http://www.aidsmeds.com/articles/hiv_miltefosine_macrophages_1667_13933.shtml. AIDSmeds.com. 2008-02-01. Accessed February 2, 2008. Archived https://web.archive.org/web/20080212122209/http://www.aidsmeds.com/articles/hiv_miltefosine_macrophages_1667_13933.shtml from the original on 2008-02-12
25. Garg R, Tremblay MJ. Miltefosine represses HIV-1 replication in human dendritic cell/T-cell cocultures partially by inducing secretion of type-I interferon. *Virology*. 2012;432:271-276. doi:10.1016/j.virol.2012.05.032
26. Sharma A, Bhomia M, Yeh TJ, Singh J, Maheshwari RK. Miltefosine inhibits Chikungunya virus replication in human primary dermal fibroblasts. *F1000Res*. 2018;7:9. doi:10.12688/f1000research.13242.1
27. Malta de Sá M, Sresht V, Rangel-Yagui CO, Blankschtein D. Understanding miltefosine–membrane interactions using molecular dynamics simulations. *Langmuir*. 2015;31:4503-4512.
28. Munoz C, Alzoubi K, Jacobi J, Abed M, Lang F. Effect of miltefosine on erythrocytes. *Toxicol Vitro*. 2013;27:1913-1919.
29. Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. *Trans R Soc Trop Med Hyg*. 2006;100:S17-S20.
30. Zhukova M, Romanenko O, Nikolaevich V. Hemolytic properties of miltefosine in liposomes of various lipid compositions. *Pharm Chem J*. 2010;44:507-509.
31. Uzunova V, Tzoneva R, Stoyanova T, et al. Dimethylsphingosine and miltefosine induce apoptosis in lung adenocarcinoma A549 cells in a synergistic manner. *Chem-Biol Interact*. 2019;310:108731.
32. Shida D, Takabe K, Kapitonov D, et al. Targeting SphK1 as a new strategy against cancer. *Curr Drug Targets*. 2008;9:662-673. PMID:18691013.
33. van Blitterswijk WJ, Verheij M, Anticancer mechanisms and clinical application of alkylphospholipids. *Biochim Biophys Acta*. 2013;1831:663-674. doi:10.1016/j.bbalip.2012.10.008
34. Kostadinova A, Topouzova-Hristova T, Momchilova A, et al. Antitumor lipids–structure, functions, and medical applications. *Adv Protein Chem Struct Biol*. 2015;101:27-66. doi:10.1016/bs.apcsb.2015.08.001
35. Ciliberto G, Mancini R, Paggi MG. Drug repurposing against COVID-19: focus on anticancer agents. *J Exp Clin Cancer Res*. 2020;39:1-9.
36. McNulty S, Flint M, Nichol ST, Spiropoulou CF. Host mTORC1 signaling regulates Andes virus replication. *J Virol*. 2013;87:912-922. doi:10.1128/JVI.02415-12
37. Stohr S, Costa R, Sandmann L, et al. Host cell mTORC1 is required for HCV RNA replication. *Gut*. 2016;65: 2017-2028. doi:10.1136/gutjnl-2014-308971.
38. Kindrachuk J, Ork B, Hart BJ, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agents Chemother*. 2015;59:1088-1099. doi:10.1128/AAC.03659-14
39. Wang CH, Chung FT, Lin SM, et al. Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. *Crit Care Med*. 2014;42:313-321. doi:10.1097/CCM.0b013e3182a2727d