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Clofazimine: A New Hope in the Battle of Corona Pandemic!

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Abstract: ***This paper aims to elucidate the role of clofazimine drug usage in the COVID-19 patients with severe respiratory distress. in thesetough times, clofazimine drugs will be acting as a boon to fight against this pandemic. Clofazimine, an antileprotic drug has anti-inflammatory property also, which hampers the release of pro-inflammatory mediators as well as suppresses the cytokine storm thus reducing the inflammation associated with novel COVID-19 viral infection and preventing the severe respiratory distress in COVID patients.***

Keywords: Clofazimine, Anti-inflammatory, COVID-19, SARS-CoV-2, Respiratory distress

1. Introduction

A new public health crisishas emerged in the world with the spread of the 2019 novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. This infection is mainly transmitted through inhalation or contact with the infected droplets[2]. The novel coronavirus can also present in the stool and in contaminated water supply and subsequent transmission via aerosolization/fico oral route is also hypothesized by various researchers [3]. The incubation period of this virus ranges from 3days to 14days after initial contact[4].The virus remains viable on surfaces for days in favorable atmospheric conditions but It can be destroyed in less than a minute by using common disinfectants like sodium hypochlorite, hydrogen peroxide,etc[5].

Studies have identified angiotensin receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa[4].It affects all age groups of the population. The most common symptoms of this infection are mild to the moderate condition are cough, sore throat, fever, fatigue, throat pain, and difficulty in breathing. In severe cases, it may progress into acute respiratory distress syndrome (ARDS), pneumonia, respiratory failure, multiorgan dysfunction and death.

Complications include acute lung injury, ARDS, shock, and acute kidney injury.The progressionof infection and worsening of symptoms are mainly associated with an extremerise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα.[6]

CLOFAZIMINE: An Antileprotic Drug.

Clofazimine is one of the compounds, which is most active in the series of the class phenazine derivative and was first synthesized by Barry and coworkers in1954[7,12]. it is synthesized by oxidizing 2-aniline using a solution of iron (III) chloride in water, which leads to the formation of 2-(p-chloroanilino)-5-(p-chlorophenyl)-3,5-dihydro-3-(iso-prophylimino)-phenazine i.e., Clofazimine. Its structure consists of phenazine substituted at the nitrogen and one of the phenyl rings with aromatic substituents.

Clofazimine is a substituted iminophenazine, which was first proposed for treating leprosy in 1962. It exerts a bactericidal effect on mycobacterium species. It belongs to the riminophenazine antibiotic class, which is a red-colored greasy dye, odorless fine powder having a melting point of 215° C and insoluble in water and possesses high lipophilic activity. Its molecular formula is $C_{27}H_{22}C_{12}N_4$ with mol. wt. of 473.41.

Pharmacokinetic Properties of Clofazimine:
The absorption rate of clofazimine was around 45-62% after oral administration[8]. It accumulates in high concentration in mesenteric lymph nodes, adipose tissue, adrenals, liver, lungs, gallbladder, bile, and spleen. it also possesses a long half-life of 70 hours. It is mainly excreted through feces, both as an unabsorbed drug and via biliary elimination.

Pharmacodynamic properties: Clofazimine exertsa slow bactericidal effect on mycobacterium species due to its action on the bacterial outer membrane[7].it appears to act as a prodrug, which is then reduced by NADH Dehydrogenase to release oxygen species, causing interference with bacterial respiratory chain and ion channels, which leads to the cidal effect. It also shows anti-inflammatory properties due to the

suppression of T-lymphocytes activity and Itincreases phagocytic activity,the oxidative metabolism of polymorphonuclear cells and macrophages.

Side effects: orange pink- brownish-black discoloration of the skin, conjunctivae and body fluids, fruit-like breath odor, dryness of skin, nausea and vomiting, irritation of the Gastrointestinal tract, skin rashes.

Contraindications and Precautions: It is avoided in pregnancy and lactating mothers, for a patient with kidney and liver problems- the dose should be modified or discontinued, should use caution ally along with diuretics -to avoid hypokalemia.

Uses:
It is used along with other antileprosy medications in the treatment of Hansen's disease. It is also used in Dapsone resistant lepromatous leprosy, erythema nodosumleprosum[9].

CLOFAZIMINE ROLE IN COVID-19 PANDEMIC:

Varieties of pharmacological approaches have been made to prevent or control or eradicate the current pandemic of COVID-19. Recent meta-analyses based on 18 randomized controlled treatment trials of "*Ivermectin"* in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and viral clearance. Similarly, "*Tocilizumab"*has also been shown to offer significant benefits in the presence of severe disease with raised inflammatory markers (CRP or IL-6) especially, when there is no improvement despite the use of steroids. Among many such proposals made to tame this pandemic in the treatment protocol or drug regimen proposed by researchers all over the world. We would like to uphold our claim of using an old-antileprotic drug "*Clofazimine"* in the treatment of the present pandemicCOVID-19.

Clofazimine is a reddish-purple-colored phenazine dye and the most common companion of dapsone or other sulphones in the treatment of leprosy. Ithas been found that dapsone the drug of par excellence for the treatment of leprosy often necessities its discontinuation due to severe allergic manifestations popularly known as lepra reactions which are further categorized as type I and II based on the aggressiveness of allergic manifestations. However, the concomitant usage of clofazimine can douse these cytokines-mediated hypersensitivity reactions and calms down inflammatory changes. This renders dapsone intolerant patients tolerant todapsone.

It is well documented in research findings that clofazimine isa cumulative drug with a very long biological half-life of 70 days. Further, it is well tolerated with minimum or mild side effects.

The clofazimine has been shown to form Biocrystals within the cytosol of macrophages where it hampers the release of the pro-inflammatory cytokines. It also exhibits significant anti-inflammatory activity to diminish lepra reactions. It is found to produce weak anti-leprotic action by inhibiting replication of leprosy bacilli through binding and inhibiting DNA templates during replication.

So, we logically anticipate that the clofazimine if administrated in the early stages of COVID-19 infection can interfere with stage IV of viral replication by intervening with the process of biosynthesis through binding to an RNA template of COVID-19 with affinity.

Further, it can also relieve the respiratory distress seen in COVID-19 by the virtue of its anti-inflammatory property as well as its ability to suppress the release of cytokines and other autocoids as mentioned above.

Thus, we strongly feel that clofazimine being well-tolerated, with favorable pharmacokinetic properties laced with its nucleic acid template binding property can prove to be a potential agent against COVID infection.

Clofazimine shows favorable safety profile processes inhibitory activity against severalcoronaviruses and can antagonize the replication of SARS COV 2 and MERS COV in a range of vitro- systems.[10]

clofazimine can inhibit proliferation and activation of T Lymphocytes through the inhibition of Na+ K+ ATPase thus it shows immunomodulatory effects with minimal side effects that could increase survival in critically ill patients infected with COVID-19 virus. [11]

It has been verified that COVID-19 carriers can be either asymptomatic or present varying degrees of severe respiratory failure in association with cytokine storm and death. Severe COVID-19 patients show an increased number of neutrophils and serum neutrophil extracellular trap Marker (NET). [13]

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References

[1] Wang C, Horby PW, Hayden FG, Gao GF, A novel coronavirus outbreak of global health concern. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)30185-9
[2] Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-Nov infection from an asymptomatic contact in Germany. N Engl J Med. 2020. https://doi.org/10.1056/NEJMc2001468.
[3] World Health Organisation. Situation reports. Available at: https:// www.who.int/emergencies/diseases/diseases/novel-coronaviruses-2019/situation-reports/.
[4] Cheng ZJ, Shan J. 2019 novel coronavirus; where we are and what we know. Infection.2020: 1-9. https: 1-9. https://doi.org/10.1007/s15010-020-01401-y.

[5] Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. J Hosp Infect. 2020 Feb 6. PII: S0195-6701(20)30046-3
[6] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan. China: a descriptive study. Lancet. 2020; 395:507-13.
[7] Cholo MC, Steel HC, Fourie PB, Germishuizen WA, Anderson R: Clofazimine: current status and future prospects. J Antimicrob Chemother. 2012 Feb;67(2):290-8. DOI:
[8] Feng PC, Fenselau CC, Jacobson RR: Metabolism of clofazimine in leprosy patients. Drug MetabDispos. 1981 Nov-Dec;9(6):521-4.
[9] Vallejo, J., Zoi, R., Banagher, M et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR- COVID-19) a randomized, double-blind, placebo-controlled trial. BMC Infect Dis 21, 635. 10.1093/jac/dkr444. Epub 2011 Oct 20.
[10] Yuan, S., Yin, X., Meng, X. et al. Clofazimine broadly inhibits coronaviruses including SARS-CoV-2. Nature 593, 418-423,2021.
[11] A Egiz, D Gala, Postgraduate medical journal, 2021.
[12] A Cavalchini, E Cozzani, A Parodi, Asian Journal of Researchin infectious diseases, 63-65, 2020.
[13] V Schmitz, JB Dos Santos- PLoS Neglected Tropical Diseases, 2021