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Research Article

High Dose Azithromycin Monotherapy as a Potential Red Blood Cell Invasion Inhibitor in Covid-19 Infected Patients

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) considered a global pandemic that threatens worldwide health and economy. Outbreaks of such emerging infections present health professionals with the unique challenge of trying to select appropriate pharmacologic treatments in the clinic with little time available for drug testing and development. with neither vaccine nor drugs are currently approved for it, the treatment is basically supportive and symptomatic and that explain why the treatment of this novel virus is very difficult. Repurposing of approved pharmaceutical drugs for new indications presents an ideal alternative solution. Recently, a published study is discussed about the use of Chloroquine and Hydroxychloroquine which are anti-malarial drugs and then the addition of antibiotics drugs such as Azithromycin which is one of the macrolide antibiotics as a combination with HCQ regimen. One of the limitations of it is increase the risk of a polymorphic ventricular arrythmia (TdP) that may be serious and potentially life-threatening. So, we looking for a safer option as Azithromycin monotherapy. In this review there will be a full elucidation behind the selection of a high dose of Azithromycin monotherapy as a potential red blood cell invasion inhibitor in COVID-19 infected patients based on studies and clinical trial showed its efficacy in such similar mechanism as in the treatment of malarial merozoites RBC invasion.

Keywords: Azalide/Macrolide antibiotic; COVID-19 prophylaxis; High dose Azithromycin; RBC invasion inhibitor; SARS-CoV-2 infection.

INTRODUCTION

SARS-CoV-2, 2019-nCoV and COVID-19 are names on trend now worldwide for the deadly pandemic novel coronavirus which was originated in bats and was transmitted to humans in Wuhan, China in December 2019 (Singhal, 2020). COVID-19 which killed many lives in all nation is part of the large corona virus family and they are RNA viruses (Richman DD *et al*, 2016). And we should note at this point that COVID-19 is not the first one of the coronavirus family to be challenging to the world as there are at least six other types of coronavirus are known to infect humans for example as almost a decade back in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected plenty of people and caused many death (WHO:MERS, 2020). COVID-19 is an acute resolved disease but it can also be deadly, with a 2% case fatality rate. Severe disease onset might result in death due to massive alveolar damage and progressive respiratory failure. (Xu *et al*., 2020) This novel coronavirus disease 2019 (COVID-19) spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, that's make the cases constantly increasing. Till now, there is no evidence from RCT to support specific antiviral drug treatment against this new pandemic (Cascella *et al*., 2020).

Knowing that the novel coronavirus 2019 has shown an ability to attacks the β-1 chain of hemoglobin as it progress in the body and captures the porphyrin to inhibit human heme metabolism and this lead to dissociate the iron to form the porphyrin this attack will cause less and less hemoglobin that can carry oxygen and carbon dioxide thus the lung cells will have extremely intense poisoning and inflammatory due to the inability to exchange carbon dioxide and oxygen frequently (Wenzhong and Hualan. 2020). Which eventually results in infection in respiratory system such as severe pneumonia, RNAemia (the RNA type virus) and acute respiratory distress syndrome ARDS, combined with the incidence of ground glass opacities (Hussin A *et al*. 2020). Now as the result of this viral attack at early phase that is similar to the merozoites invasion the invasion of the virus to the blood cell the

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viral protein will infects hemoglobin by the immune hemolysis of red blood cells (Wenzhong and Hualan. 2020). And as a consequence and results of the RBC hemolysis and hemoglobin reaction, the release of iron from Hgb will occur (Wenzhong and Hualan. 2020).

Azithromycin is semi-synthetic of the azalide, derived from erythromycin, and a member of a subclass of macrolide antibiotics with mostly bacteriostatic activities. It is used to treat certain bacterial infections, most often bacteria causing middle ear infections, tonsillitis, throat infections, laryngitis, bronchitis, pneumonia, and sinusitis. It is also effective against certain sexually transmitted infectious diseases, such as non-gonococcal urethritis and cervicitis. Several studies have shown the safety profile of azithromycin even if used in high doses as used in early stage of malaria pathogenesis (inhibit the merozoite invasion into RBCs) , this is in a relationship with pathogenesis of COVID-19 which invades the RBCs and causes RBCs hemolysis, hemoglobin reaction , release of iron from hemoglobin ,and result in some disease like Iron overload-Hyperoxidative stress-Radical storm status, ARDS, and DIC. In this review we propose the use of high dose of Azithromycin 500-1000 mg once daily as an interventional monotherapy treatment in early COVID-19 infected patients that are intolerance to HCQ.

DISCUSSION

The role of erythrocytes in the pathophysiology of COVID-19 is under-estimated; the co-efficient of variation of red blood cell distribution width (RDW) is predictive of severity of disease state. Elevated RDW is correlated with reduced erythrocyte turnover; red blood cells become smaller as they age and the delay in clearance expands the low-volume tail of the volume distribution. Suppressed erythrocyte turnover may indicate erythropoietin distress and function as a compensatory mechanism to maintain circulating red blood cell levels. Excess porphyrins in red blood cells can precipitate cell lysis and development of hemolytic anemia susceptibility to COVID-19 appears to be determined by blood group; blood group A is most affected whereas blood group O seems to be protected. Clinical evaluation of Wuhan patients reveals hemoglobin levels below the normal range in most patients as well as increased total bilirubin and elevated serum ferritin. Hyperbilirubinemia is observed in acute porphyria and would be consistent with ineffective erythropoiesis and rapid hemoglobin turnover. Since hemoglobin is a significant source of superoxide generation in RBC and since there is an electron transfer in the interaction between the heme iron and oxygen in oxygenated Hb, the heme iron normally remains in the Fe(II) ferrous state but any alterations in this exchange like in Hb auto-oxidizes this result in the formation of metHb which is the ferric Fe(III) and superoxide thus hyper-oxidative stress state in patients and may lead to DIC (fibach *et al*. 2008). Elevated serum ferritin levels are typical of acute porphyria and would be expected upon dissociation of iron from heme. as a summary, the Pathogenesis of COVID-19 after invasion of RBCs leads to RBC hemolysis, hemoglobin reaction, release of Iron from hemoglobin, Hyper-Oxidative stress, ARDS, DIC, and high ferritin level which correlates with high mortality levels (Cron & Chatham, 2020). So, investigation of infection markers in patients with severe and very severe COVID-19, including high ferritin (Zhou *et al*. 2020). And from here we can say that since ferritin level is an easy laboratory marker it could be used as a surrogate marker and indicator for the rate and severity in COVID-19 patients.

RBCs invasion that happens in COVID-19 patients is similar to what happens in malaria. In contrast to many other pathogenic organisms, Plasmodium spp. can efficiently infect their hosts by rapidly gaining entry to cells using their own invasion apparatus to identify, penetrate, and establish themselves. In this review, we address the mechanisms that these parasites utilize for erythrocyte invasion with strong emphasis on P. falciparum, but we draw on lessons learned from related parasites. The phylum Apicomplexa includes parasites of human and veterinary importance such as Toxoplasma, Theileria, Eimeria, Babesia, and Cryptosporidium. All apicomplexan parasites share features including presence of a specialized apical complex, which is central to the invasion process. The Plasmodium-infected mosquito injects sporozoite forms into the human host, and these migrate to the liver and invade hepatocytes within which they develop into liver merozoites. These merozoites are released into the bloodstream, where they invade erythrocytes. The free merozoite is then able to invade other erythrocytes (Cowman & Crabb, 2006). Azithromycin marks one of the few clinically used compounds that have been shown to inhibit the RBC invasion of merozoite of malaria (Wilson *et al*. 2015). Noting that although Azithromycin is a macrolide antibiotic, it has clinically shown that Azithromycin could have invasion-inhibitory activity against malaria parasites (Burns *et al*. 2019). It has shown the ability to target the malaria parasite's remnant plastid called the apicoplast and the inhibition of the apicoplast ribosome prevents the replication of malaria essential organelle resulting in the loss of isoprenoid pyrophosphate (IPP) which is precursor synthesis and malaria death occur in a full two cycles of growth (which we can conclude a delayed death) post treatment with Azithromycin (Burns *et al*. 2019). Anyway, despite the slow malaria killing activity of Azithromycin, recently data showed that 250-fold higher concentration of Azithromycin can rapidly inhibit RBC invasion of merozoite *in vitro* which considered an early step of malaria pathogenesis in human and this activity has nothing to do and independently of apicoplast-targeted delayed death

done by Azithromycin mentioned before (Burns *et al*. 2019).

The safety profile of the Azalide antibiotic, Azithromycin, has been assessed in 3,995 patients and Azithromycin had no marked or consistent effect on laboratory safety parameters (Europe PMC, 2019). For more than decade, Azithromycin has been used to treat upper respiratory tract infections in infants and children. Azithromycin has a number of unique pharmacokinetic properties that provide opportunities for the development of new and potentially more effective dosing strategies. The big differences in labeled doses of Azithromycin have led to further exploration of dosing flexibility. Azithromycin is characterized by an extraordinarily long mean residence time in vivo and a tissue rather than plasma concentration basis for its clinical activity. These properties suggest that the activity of the drug might be enhanced when used in high dose, short course regimens (Hopkins, 1991). Azithromycin has significantly fewer side effects than comparator antibiotic drugs. When it is used once daily for 5 days, it produced a satisfactory therapeutic outcome similar to those of given co-amoxiclav TID for 10 days for treatment of community-acquired pneumonia (Harris *et al*., 1998).

CONCLUSION

Azithromycin at high dose has the ability to inhibit the merozoite invasion of malaria spp. and from Azithromycin's history of safety, proven activity and its long half-life (>50 hours), we highlight a novel idea for treatment HCQ in tolerated/contraindicated COVID-19 infected patients by using **High Daily Dose of Azithromycin Monotherapy (500 mg-1000 mg) Strategy for 5 days.** This strategy could act as an interventional treatment in early COVID-19 infected patients as RBC invasion inhibitor before COVID-19 viruses detach iron from hemoglobin molecules. To elucidate this proposed Anti-COVID-19 modality, further robust, controlled, randomized clinical trials are required.

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