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Treatment of COVID-19 in G6PD deficient patients: A review

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The disease caused by the novel corona virus (COVID-19) has been declared a pandemic by the World Health Organization (WHO). The virus spreads fast, is highly contagious, and transmits through respiratory droplets and direct contact. The symptoms are dyspnea, myalgia, fever and, in later stages, acute respiratory distress syndrome. The number of cases is increasing, creating an urgent need to find a vaccine and treatment for prevention and control. Various drugs are redirected as a possible application in COVID-19. Hydroxychloroquine (HCQ), an antimalarial drug, a promising agent, is used for prophylaxis as well as for treatment. However, for patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency, the treatment may cause adverse events. It is known that antimalarial treatment causes hemolytic anemia in G6PD deficient patients. In this review, we reviewed the safety of HCQ prescribed for patients who are G6PD deficient and COVID-19positive. According to literature, HCQ has a good safety profile with less side effects and the risk of hemolytic anemia in G6PD deficient patients is also lower. In addition, HCQ is cheaper and easily available, in contrast to other drugs used against COVID-19. As one of the few current treatments showing an effect against COVID-19 by reducing the viral replication and decreasing its infectivity, HCQ can be considered as a safe treatment modality. However, prior testing for G6PD deficiency must be done in COVID-19 positive patients.

Keywords: COVID-19; Hydroxychloroquine; Hemolytic anemia; G6PD

INTRODUCTION

The novel coronavirus (COVID-19) has emerged as a pandemic affecting the whole world. Corona viruses have caused epidemics in the Middle East and China, known as Middle East respiratory syndrome (MERS CoV) and severe acute respiratory syndrome (SARS-CoV-1) in China respectively. SARS was first identified in China in 2002 (Lee et al. 2003), and MERS during the 2012 summer season in Jeddah, Saudi Arabia

(Zaki et al. 2012). The coronavirus is responsible for a group of zoonotic diseases in humans. In late December 2019, a new virus belonging to the coronavirus group, was detected in China. The outbreak was reported in a seafood market in Wuhan in China. The market was sterilized and closed by the local government in Wuhan to prevent further transmission. This virus is known to cross species and cause disease, especially upper respiratory tract infection and pneumonia (Raoult et.al. 2020).

Novel Coronavirus 2019 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus. The transmission of COVID-19 from human to human occurs through respiratory droplets and direct contact routes and it is transmissible through asymptomatic patients (Chan et al. 2020).

The most frequent symptoms at the onset of the illness are fever, cough, and myalgia or fatigue with stuffiness of the nose, pharyngalgia and diarrhea (Chen et al. 2020a). Asymptomatic patients may not be detected initially but may have symptoms such as fever, headache, dyspnea and fatigue (Huang et al. 2020). Severe patients may have dyspnea and hypoxemia one week after the onset, which could progress to acute respiratory distress syndrome (ARDS). (Patel et al. 2020).

In addition to cough, dyspnea and other symptoms, anosmia and hyposmia were observed in 30% of patients with COVID-19. A few studies state that the loss of smell may be due to the penetration of the coronavirus through the olfactory epithelium into areas of brain and also from the cribriform plate of the ethmoid bone, which can result in cerebral involvement (Barnett and Perlman,1993; Youngentob et al. 2001; Netland et al. 2007). Other studies mentioned that the neurological involvement occurs in 36.4% of COVID-19 cases, which has been divided in three categories: central nervous system (CNS) diseases, peripheral nervous system (PNS) diseases, and skeletal muscle disorders. CNS disease includes headache, dizziness, acute cerebrovascular disease, and epilepsy, and PNS disease consists of anosmia, hyposmia and hypogeusia (Zhou et al. 2020; Fanouriakis et al. 2020; Fanouriakis et al. 2019).

For patients to meet the diagnostic criteria, the samples are taken by nasopharyngeal and oropharyngeal swabs, and if possible, from the lower respiratory tract, including sputum and broncho-alveolar lavage (Patel et al. 2020). Laboratory findings include lymphopenia, prolonged prothrombin time, elevated lactate dehydrogenase, elevated aspartate aminotransferase, elevated creatine kinase, creatinine, and elevated C-reactive protein (Huang et al. 2020; Wang et al. 2020). Most of the patients have abnormal CT findings, showing multifocal, patchy ground-glass opacities, frequently near the peripheral sections of the lungs (Chan et al. 2020). Patients who develop severe disease progress from mild to severe bilateral multiple lobular lung opacities (Chung et al. 2020).

Currently, there is no approved treatment or vaccine for COVID-19 (Vijayvargiya et al. 2020). Treatment is symptomatic with oxygen therapy in severe cases. Mechanical ventilation is used in cases of severe pneumonia and respiratory failure and hemodynamic support is required in the management of septic shock. General treatment for COVID-19 patients includes bed rest and supportive treatment, monitoring vital signs (such as respiratory rate, heart rate, blood pressure and oxygen saturation), ensuring sufficient energy intake and also maintaining a constant internal environment (water, electrolytes, and other internal environment factors) (Cascella et al. 2020).

Non-pharmacological measures generally include wearing a mask, face shields, and maintaining social distancing. The government of every country is taking appropriate measures in terms of a complete lockdown and enforcing social distancing. For healthcare workers, personal protective equipment (PPE) such as face shields and safety glasses are used as precautionary measures. (Derek et al.2020)

Various randomized clinical trials are being conducted to find a treatment modality for COVID-19. Several therapeutic options have been repurposed for COVID-19, including lopinavir/ritonavir (400/100 mg every 12 hours), chloroquine (500 mg every 12 hours), and hydroxychloroquine (200 mg every 12 hours). Alpha-interferon (for example 5 million units by aerosol inhalation twice per day) is also used (Cascella et al. 2020). Another drug, Remdesivir, an inhibitor of RNA polymerase activity, has shown activity against the Ebola virus and is also being tested against COVID-19 (Gordon et al. 2020). It had positive results in a rhesus macaque model of MERS-CoV infection (Wit et al. 2020).

Currently, hydroxychloroquine (HCQ) is widely used as a COVID-19 prophylactic as well as for slowing the progression and development of pneumonia in symptomatic patients. HCQ has antimalarial and anti-inflammatory activity, as well as antiviral properties (Singh et al. 2020). However, a major concern for antimalarial drugs are patients suffering from glucose-6-phosphate dehydrogenase (G6PD) deficiency. In this literature review, we explored the suitability of HCQ as treatment for COVID-19in G6PD deficient patients.

G6PD Deficiency

G6PD deficiency is an X-linked genetic disorder, which results in hemolysis after antimalarial treatment. Of the existing G6PD deficiencies, the Mediterranean type is severe, with the African variant a mild type of G6PD deficiency. The mild type of variant is most frequently seen in African-Americans and the severe form in Europe and Asia (Beutler, 1996; Ashley et al. 2014). It was first noted during the clinical trials of primaquine as causing hemolysis. The absence of G6PD results in excessive oxidative stress due to the generation of free radicals causing hemolysis of red blood cells (RBCs) (Beutler, 2008; Alving et al.1956). The global prevalence of G6PDdeficiency is 4.9% (Nkhoma et al. 2009).

G6PD catalyzes the rate limiting step of the hexose monophosphate pathway for pentose phosphate synthesis. Nicotinamide adenine dinucleotide phosphate (NADPH) is required for this pathway, which maintains various biosynthetic reactions required for maintaining intracellular glutathione and other sulfhydryl groups in its reduced form. NADPH is required to maintain internal cell stability to withstand the free radicals and oxidative stress (Kurutas. 2016). Depending upon the degree of enzyme deficiency, the clinical symptoms are classified, patients with severe enzyme deficiency, experience hemolysis and anemia (Table 1) (WHO, 1967).

Table 1 Classification of G6PD deficiency according to the percentage of enzyme activity

Class	Enzyme activity
Class I	Severely deficient associated with chronic non-spherocytic anemia
Class II	Severely deficient <10% residual enzyme activity
Class III	Moderately deficient, 10-60% enzyme activity
Class IV	Near normal or normal enzyme activity, 60-150% enzyme activity
Class V	Enzyme activity >150%

Class I is associated with severely deficient enzyme activity, resulting in non-spherocytic anemia with a higher possibility of hemolytic anemia. In class II-class V, the enzyme activity increases and the risk of hemolysis decreases. Class V is the most enzymatically active with a lower possibility of hemolysis (Francis et al. 2013).

Acute hemolytic anemia is caused in mature RBCs, deficient of NADPH and a reduced form of glutathione resulting in uncompensated oxidant stress in erythrocytes, which causes the conversion of oxyhemoglobin to methemoglobin (Beutler,1983). Drugs such as primaquine, sulphonamides, nitrofurantoin and several anti-inflammatory agents possess oxidant properties and they are most frequently associated with hemolysis (Greene,1993). The first occurrence of hemolytic anemia was seen with primaquine used in G6PD deficient patients. All antimalarial drugs should be used cautiously. In terms of the current pandemic, HCQ and chloroquine has been repurposed for use and has shown some promising activity against COVID-19 (Wu et.al. 2020)

Hydroxychloroquine (HCQ)

HCQ is an approved antimalarial drug and used for the last 70 years. It also has other properties. HCQ is the first line drug therapy for systemic lupus erythematosus and it efficiently cures various diseases such as joint pain, rashes, thromboembolic events and also increases the survival rate (Canadian Hydroxychloroquine Study Group, 1991). Various mechanisms have been proposed for its antiviral activity against corona virus infection. The corona virus binds to an angiotensin converting enzyme (ACE2) receptor and invitro studies indicate that prior exposure of chloroquine to vero cells affected the glycosylation process of ACE2 receptors, resulting in prophylaxis from infection, the probable mechanism of action for its prophylactic use (Savarino et al. 2003). In epithelial lung cell cultures, chloroquine is reported to inhibit the invitro replication of HCoV-229E (Blau and Holmes, 2001; Kono et al. 2008). It also inhibits the viral particle glycosylation. There are two proteins, membrane protein M and spike protein S and the S protein is damaged if there is lack of glycosylation, which is required for receptor binding (Savarino et al. 2004; Kirchdoerfer et al. 2016; Ujike and Taguchi, 2015)

Another postulated mechanism of action of chloroquine is inhibition of quinone reductase 2, involved in the synthesis of silica acid. This acid is a monosaccharide acid found at the extremity of sugar chains present on a transmembrane protein and required for ligand recognition. Since silica acid moieties are used by corona virus and orthomyxovirus as receptors, this could explain the antiviral effect of chloroquine and its derivatives (Devaux et al. 2020).

Chloroquine also disturbs the pH of the cell and disturbs the pH dependent entry of coronavirus. It also impairs the viral infectivity. In addition, there was a decrease in the transmission of the disease in the post-infection period after treatment with chloroquine (Yao et al. 2020). Chloroquine inhibits the phosphorylation (activation) of the p38 mitogen-activated protein kinase (MAPK) in THP-1 cells as well as caspase-1 required for viral replication (Seitz et al. 2003).

HCQ also has immunomodulatory activity, which inhibits the activation of the Toll like receptor pathway signaling and cytokines production. This process suppresses the pathway, which decrease the cytokinins production and prevents the conversion of mild respiratory disease to severe disease. HCQ is known to have a high concentration in lung and brain tissue, which is advantageous for using it in COVID-19 (Picot et al. 2020).

DISCUSSION

Various drugs have been redirected to determine its effect against COVID-19. The beneficial effect of antiviral therapy was observed in SARS-CoV in a pilot clinical trial (Loutfy et al. 2003). The disadvantage of those drugs is that their efficacy and safety in COVID-19 is still being tested. In addition, the treatment is costly compared to HCQ and the safety and efficacy in G6PD deficiency is still unclear. A few studies have been done with HCQ in this regard. HCQ is inexpensive and easily available, as well as recommended for prophylaxis and treatment of COVID-19. HCQ is known to penetrate into the CNS from studies conducted in glioblastoma patients; patients were treated safely with a dose of 600 mg with an adjuvant (Rosenfeld et al. 2014).

The recommended total dose for its antimalarial activity is 1500 mg according to the CDC treatment guidelines for malaria. In a study conducted with children with interstitial lung disease, when treated with HCQ as monotherapy, the symptoms resolved in 14 of 16 patients. The dose used was 3.5-10 mg/kg body weight/day with a maximum dose of 600 mg/day. HCQ was well tolerated in the children with fewer side effects (Braun at al. 2015).

In a small randomized study with 36 patients suffering from COVID-19, a higher clearance of the virus in the HCQ treated group compared to the control on Day 6 was reported. The dose of HCQ was 200 mg 8 hourly for 10 days. Six patients received Azithromycin which showed clearance, but the difference was not statistically significant. In the study, they provided evidence that a nasopharyngeal carrier of the virus is cleared within 3 to 6 days of HCQ treatment, which has a safer dose dependent toxicity profile compared to chloroquine (Gautret et al. 2020).

Another study with 30 COVID-19 positive patients, indicated that throat swabs became negative faster compared to the control. Due to the small sample size, a study with a large sample size is required to provide strong evidence (Chen et al. 2020b). A study conducted in China reported that 100 infected patients, treated with chloroquine, experienced a rapid decrease in fever and symptoms and improvement in their lung CT images. The time to recovery was shorter and no serious adverse events were seen. The drug has been included in the SARS-CoV-2 treatment guidelines in China (Gao et al. 2020; Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia, 2020)

A recent study by Million stated that a cohort of 1061 COVID-19 patients were treated with a HCQ and Azithromycin combination. They concluded that the combination is safe and effective in patients diagnosed withCOVID-19, and that the mortality rate reduced to 0.5% in elderly population. (Million et al. 2020)

Various clinical trials are being conducted for example, chloroquine vs placebo in healthcare settings NCT04303507, post-exposure prophylaxis for COVID-19 with HCQ vs placebo NCT04308668, HCQ vs placebo for chemoprophylaxis in healthcare personnel in contact with COVID-19 patients (PHYDRA trial) NCT04318015 (Agrawal et al. 2020).

Various studies indicate that chloroquine does not cause hemolysis in mild G6PD deficiency, which is most likely self-limiting and non-life threatening unless trigger factors for hemolytic anemia are present. In severe forms of G6PD deficiency, it has to be used cautiously (Beutler et al. 2007). Various others adverse effects have been noted with the use of HCQ, such as retinopathy, cardiovascular events and cardiomyopathy. Retinopathy is seen in cases treated with HCQ for more than 5 years. Should there be a risk for cardiomyopathy, an ECG before the initiation of treatment is recommended (Krishna and White,1996; Jorge et al. 2018)

Similarly, a review of 275 patients found only 11 patients with G6PD deficiency, with two experiencing hemolysis, not related to the HCQ exposure. The author claimed the study to be the largest in United States with using HCQ in G6PD deficient patients, however, most of the patients had the mild form of G6PD deficiency (Mohammad et al. 2018). In another study with 20 children, 2 patients developed hemolytic anemia. Chloroquine was prescribed with chloramphenicol and aspirin for one patient and for the second, only chloroquine and chloramphenicol. No study reported the incidence of hemolytic anemia with a monotherapy of HCQ. In a review it was stated that though caution is mentioned in the package insert, it has not been mentioned in any textbooks. Precaution should be taken in cases where HCQ is combined with other agents that could cause hemolytic anemia (Youngster et al. 2010). A study was conducted with 74 patients to explore the safety of combining chloroquine with methylene blue in G6PD deficient patients. A3-day oral course of chloroquine with methylene blue was given with a total dose of chloroquine of 1500 mg and 780 mg of methylene blue. No hemolysis occurred. The study concluded that chloroquine is safe in G6PD deficient healthy men in West Africa (Mandi at al, 2005). Limited data is available on HCQ use in COVID-19 patients.

CONCLUSION

COVID-19 is a global threat, and the pandemic must be controlled. Various drugs are being repurposed for application in this disease. HCQ is a promising agent with a positive safety profile and could be tested in COVID-19 patients with G6PD deficiency.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

AA wrote the manuscript. KA and MZ helped in the writing and designing of the manuscript. KA, MA and NB collected the data and participated in coordination. LA carried out the pharmacological information. AA, KA, AR, KS, and TA supervised and reviewed the final manuscript. AA is the project leader. All authors read and approved the final version**.**

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