European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2020; 24: 7923-7924

Letter to the Editor

Hydroxychloroquine (HCQ) use in G6PD deficient COVID-19 patients and the risk of Acute Hemeolytic Anaemia (AHA)

Dear Editor,

Hydroxychloroquine (HCQ) primarily used to treat systemic lupus erythematosus (SLE) and malaria among others, is currently used to improve the pneumonia symptoms in critically ill COVID-19 patients[1], taking cue from recent reports suggesting that HCQ could reduce the viral load in patients with COVID-19 combined with azithromycin[2]. Without going into ambiguity about the peer review and low sample size of the study, we would like to address some potential safety issues associated with the use of hydroxychloroquine, especially in the critically ill ones.

Accumulating evidence suggests that sepsis onset in COVID-19 is causing red blood cell (RBC) lysis through lipid peroxidation of the RBC membrane, alteration of RBC membrane pumps, an influx of calcium into the RBC, and changes in 2,3-diphosphoglycerate levels, releasing intracellular content leading to persistent inflammatory conditions and multiple organ failure[3]. Existing oxidative status in COVID-19 patients coupled with hematologic effects like aplastic anemia, agranulocytosis, leukopenia and thrombocytopenia of chloroquine can lead to oxidant hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency[4].

Elucidation of a probable genetic determinant contributing to the differential susceptibility to COVID-19 infection remains to be done. However, G6PD deficiency, an X-linked enzymatic disorder, may render an individual susceptible to SARS-CoV2 infection. G6PD catalyzes the pentose phosphate pathway ultimately producing adenine dinucleotide phosphate (NADPH) molecule, which is essential in RBCs. Of all, RBCs lacking other NADPH-producing enzymes are particularly susceptible to damage by reactive oxygen species.

Early evidence indicate that the absence of the bioactive G6PD enzyme led to 12 fold production and 3 fold replication of HCov-229E coronavirus, *in vitro*[5], strongly suggesting that G6PD-deficient COVID-19 patients may suffer highest chloroquine induced toxicity. Reports about the global prevalence of G6PD lacks consensus; however, the estimate put it around 7%[6] with differences among different ethnic groups. Exposure of G6PD deficient individuals to oxidative stressors can induce acute hemolysis. It is safe to assume that the use of chloroquine in critically ill G6PD deficient COVID-19 patients can increase the disease severity.

Way Forward

Testing for G6PD deficiency among hospitalized patients with COVID-19 disease is warranted before the results of Phase III clinical trial of hydroxychloroquine in COVID-19 patients are available[7]. Additionally, recombinant human erythropoietin (rhEPO) to increase the red cell mass can be used for anemia correction in COVID-19 patients[8]. Recent reports indicate that EPO protects many organs including lung, kidney and nervous system against ischemia and apoptosis[9] in critically ill patients[10]. EPO also reduces pro inflammatory IL-6, an important constituent of cytokine storm, and Hepcidin production, in turn downregulating cellular ferroportin and iron absorption[11], that can lead to efflux of iron from macrophages. It seems likely that alveolar macrophages phagocytose the SARS-CoV2 viral particles and this iron efflux may hamper the enzymatic activities and eventual infection of T lymphocytes[12]. Therefore, we recommend G6PD testing before using HCQ. Further, rhEPO administration in anemic COVID-19 patients may be considered.

Corresponding Author: Naseem Akhter, Ph.D; e-mail: naseem.du@gmail.com

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Taccone FS, Gorham J, Vincent JL. Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base. Lancet Respir Med 2020; 8: 539-541.
2) Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, Doudier B, Courjon J, Giordanengo V, Vieira VE, Tissot Dupont H, Honoré S, Colson P, Chabrière E, La Scola B, Rolain JM, Brouqui P, Raoult D. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 Mar 20:105949.
3) Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, Vincent JL. Red blood cell rheology in sepsis. Intensive Care Med 2003; 29: 1052-1061.
4) Pharmacists TASoH-S. Hydroxychloroquine Sulfate Available: https://www.drugs.com/monograph/hydroxychloroquine-sulfate.html. Accessed 21.04.2020, 2020.
5) Wu YH, Tseng CP, Cheng ML, Ho HY, Shih SR, Chiu DT. Glucose-6-phosphate dehydrogenase deficiency enhances human coronavirus 229E infection. J Infect Dis 2008; 197: 812-816.
6) Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. Blood Cells Mol Dis 2009; 42: 267-278.
7) Novartis. Novartis to sponsor large clinical trial of hydroxychloroquine in hospitalized COVID-19 patients Available: https://www.novartis.com/news/media-releases/novartis-sponsor-large-clinical-trial-hydroxychloroquine-hospitalized-covid-19-patients. Accessed 21st April 2020, 2020.
8) Hadadi A, Mortezazadeh M, Kolahdouzan K, Alavian G. Does recombinant human erythropoietin administration in critically ill COVID-19 patients have miraculous therapeutic effects? J Med Virol 2020; 92: 915-918.
9) Nekoui A, Blaise G. Erythropoietin and nonhematopoietic effects. Am J Med Sci 2017; 353: 76-81.
10) French C. Erythropoietin in critical illness and trauma. Crit Care Clin 2019; 35: 277-287.
11) Ganz T. Iron and infection. Int J Hematol 2018; 107: 7-15.
12) Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol 2008; 6: 541-552.

S.A. Dar[1], M. Wahid[1], S. Haque[1], S.S. Almalki[2], N. Akhter[2]

[1]Research and Scientific Studies Unit, College of Nursing and Allied Health Sciences, Jazan University, Jazan, Saudi Arabia
[2]Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University, Al Bahah, Saudi Arabia