Received: 4 May 2020 | Revised: 27 May 2020 | Accepted: 28 May 2020

DOI: 10.1111/ejh.13460

European Journal of Haematology WILEY

LETTER TO THE EDITOR

Doubtful precipitation of hemolysis by hydroxychloroquine in glucose-6-phosphate dehydrogenase-deficient patient with COVID-19 infection

Dear Editor,

We read with great interest the recent article by Beauverd et al[1] on an interesting case of severe hemolysis in a patient with COVID-19 treated with hydroxychloroquine. The authors concluded that COVID-19 infection was possibly the initial trigger for hemolysis. However, the article also suggested that hydroxychloroquine possibly worsened the hemolysis, and further cautioned the use of hydroxychloroquine in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients. We would like to comment on the authors' attribution of accentuated hemolysis to the use of hydroxychloroquine.

There are some discordances between the text and the figures in the data presented by Beauverd et al.[1] In the figure, the lowest hemoglobin (nadir) appears to be 6.5 g/dL on day-7 while the same was mentioned as day-6 in the text. This becomes extremely important when considering the temporal relationship between hydroxychloroquine administration and accentuation of ongoing hemolysis. As the authors illustrate, the index patient with G6PD deficiency having COVID-19 infection and other comorbidities had a progressive and massive drop in plasma hemoglobin (12 g/dL on day-1 to 6.5 g/dL on day-7—as per the figure). Biological signs of hemolysis like ghost cells and raised LDH were already present by day-5 (before starting hydroxychloroquine). It should also be noted that the authors mentioned the rise in "direct" bilirubin—while hemolysis usually leads to a rise in "indirect" bilirubin. The peripheral blood smear anomalies that are orientated with a G6PD deficiency diagnosis, such as hemi-ghost cells, were increasing from day-4 until day-7 (one day after administration of single large dose of hydroxychloroquine). Based on these factors, one can safely ascertain that hemolysis (and hemolytic parameters) gradually increased from day-1 to reach the peak around day-7 followed by a gradual improvement. The improvement of hemoglobin, hemi-ghost cells, and bilirubin by day-8 (2 days after drug intake) seems to contradict the possibility of the single hydroxychloroquine dose accentuating the ongoing hemolysis. The contribution of multiple blood transfusions, initiated on the day of hydroxychloroquine administration, toward the abnormal hemolytic parameters should also be considered. There is also emerging evidence on the complement-mediated pro-coagulated state, a pre-requisite for atypical hemolytic-uremic syndrome (aHUS), in COVID-19.[2] It will be of benefit to the readers if the authors had presented any data on haptoglobin, plasma hemoglobin levels, liver function tests, and coagulation parameters to exclude other possible causes of hemolysis such as disseminated intravascular coagulation. We fully agree with the authors' conclusion that hemolysis is possibly precipitated by severe COVID-19 infection and that more reports of hemolysis associated with COVID-19 will possibly emerge in the future. In short, the introduction of hydroxychloroquine seems merely an incidental association with ongoing hemolysis associated with the COVID-19 infection.

We would also like to elaborate on the controversy of hydroxychloroquine use in G6PD-deficient individuals. The recent US Food and Drug Administration's[3] COVID-19 specific warning regarding potential cardiotoxicity with hydroxychloroquine use, mentions G6PD as a baseline test for starting hydroxychloroquine. However, a recent meta-analysis of clinical trials in chloroquine (the parent drug of hydroxychloroquine) +/− primaquine, did not demonstrate a significant drop in hemoglobin from baseline in G6PD deficients on chloroquine monotherapy.[4] As the authors have rightly mentioned, there are no guidelines that recommend baseline G6PD evaluation for hydroxychloroquine prescriptions.[5] The presumed caution on using hydroxychloroquine in G6PD deficients is not supported by clinical evidence, but by drug information resources and drug package inserts.[6] In an evidence-based review on medications mentioned in 3 major medical textbooks as contraindicated in G6PD deficiency, Youngster et al[7] have concluded that chloroquine monotherapy is safe in G6PD deficients. Notably, William's textbook of hematology considers no contraindications for chloroquine use in G6PD deficients.[7] It should also be noted that there are currently no available reports of hemolysis in G6PD-deficient individuals with hydroxychloroquine or chloroquine monotherapy.[6,7]

Infections are the most common triggers for hemolysis in G6PD deficiency.[7] Given that the index patient with COVID-19 infection had significant hemolysis even before administration of the single dose hydroxychloroquine, along with the lack of previous reports of hemolysis with the same, an association of accentuation of hemolysis with hydroxychloroquine seems unlikely. In this light, attributing hemolysis to hydroxychloroquine in the context of G6PD deficiency needs further evidence.

CONFLICT OF INTEREST

We declare no competing interests.

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