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Name of journal: *World Journal of Experimental Medicine (WJEM)*

Manuscript NO.: 85302, Letter to the Editor

Title: **The ophthalmologic implications to consider when using hydroxychloroquine to treat COVID-19 infection and induced arthritis**

Dear Editor-in-Chief of WJEM,

I would like to extend my gratitude for the efforts and time spent reviewing the submission. The Reviewers make excellent points and offer valuable suggestions to improve the manuscript. **Please find the responses in bold font under each of the comments made by the reviewer below, which can also be found in red font in the revised manuscript:**

Reviewer 1

Thanks for writing up this review. It is comprehensive. Please add in an additional citation for the Bull's eye maculopathy mentioned: Au SCL. Hydroxychloroquine retinal toxicity: The bull's eye in the human eye. Vis J Emerg Med. 2020 Oct;21:100818. doi: 10.1016/j.visj.2020.100818. Epub 2020 Jun 25. PMID: 32835115; PMCID: PMC7315151.

Many thanks for the thorough review of the letter. The suggested publication regarding Bull's eye maculopathy provides important considerations about this condition. Mention regarding notions presented in this paper have been added and have been cited under the bibliographic reference #20 as follows:

“According to studies, the medication impacts the metabolism of retinal cells and binds to melanin in the RPE, which may help to explain why some people continue to experience side effects even after stopping the prescription. With regards to dysfunction related to toxicity, it is thought that HCQ binds to melanin in the RPE, blocking its function, which can lead to irreversible photoreceptor loss and resulting visual field defects over the afflicted sector of the retina. In some cases, Bull's eye configuration can be seen as a ring scotoma on a visual field test when RPE malfunction leading to atrophy occurs across the perifoveal ring when the central fovea is spared.[20]

Reviewer 2

1. Lack of clear evidence: The article mentions that HCQ has been proposed as a treatment for COVID-

19, but there is no clear evidence to support this claim. The article does not provide any references or studies that demonstrate the effectiveness of HCQ in treating COVID-19.

The aim of the Letter to the Editor was to comment on the ophthalmologic considerations of using HCQ for COVID-19, which was published in a paper previously published. This letter was not intended to discuss the effectiveness of HCQ in treating COVID-19. The following phrase has been added in the introduction to clarify this point:

“The aim of this letter article was to summarize the important ophthalmologic considerations when HCQ is considered in the treatment of COVID-19. The issues regarding whether or not HCQ is effective in treating COVID-19, which was reported in the papers recently published in this journal,[1,4] will not be considered in this article.”

2. *Limited information on the mechanism of retinal toxicity: The article mentions that HCQ can cause retinal toxicity, but it does not provide a detailed explanation of the mechanism behind this toxicity. The article only mentions that it is thought to be due to the accumulation of the drug in the retinal pigment epithelium, without providing further details.*

With regards to retinal toxicity, the following details have been added with an appropriate bibliographic citation:

“It is yet unclear how HCQ can cause retinal damage. According to studies, the medication impacts the metabolism of retinal cells and binds to melanin in the RPE, which may help to explain why some people continue to experience side effects even after stopping the prescription. With regards to dysfunction related to toxicity, it is thought that HCQ binds to melanin in the RPE, blocking its function, which can lead to irreversible photoreceptor loss and resulting visual field defects over the afflicted sector of the retina. In some cases, Bull's eye configuration can be seen as a ring scotoma on a visual field test when RPE malfunction leading to atrophy occurs across the perifoveal ring when the central fovea is spared. The half-life of HCQ is about 1 month, which a washout period of about 6 months. Early diagnosis of HCQ retinal toxicity is crucial to prevent maculopathy from progressing after HCQ use is stopped.[20]”

3. *Lack of information on the study design: The article does not mention the design of any studies that have investigated the use of HCQ in treating COVID-19. It is unclear whether these studies were randomized controlled trials or observational studies, and whether they had any methodological limitations.*

As mentioned in point 1, the aim of this brief Letter to the Editor was to strictly comment on the ophthalmologic considerations of using HCQ for COVID-19. This letter was not

intended to discuss the types of studies regarding HCQ in treating COVID-19.

4. Limited information on the ophthalmological adverse events: While the article mentions that HCQ can cause ophthalmological adverse events, it does not provide a comprehensive list of these events. The article only mentions retinopathy, corneal deposits, and papilledema, without providing any information on their frequency or severity. 5. Limited information on monitoring and management: While the article mentions that patients receiving HCQ should be periodically monitored for potential ophthalmological side effects, it does not provide detailed guidance on how this monitoring should be conducted. The article also does not provide any guidance on how to manage patients who develop HCQ toxicity, other than immediate termination of the drug and consideration of alternative treatment regimens. Overall, the article lacks clear evidence and detailed information on the use of HCQ in treating COVID-19 and its potential adverse effects and management strategies. More research is needed to fully understand the risks and benefits of using HCQ in this context.

The Reviewer makes valid points. The aim of this brief article, however, was not to provide a thorough and descriptive review about the ocular effects of HCQ and the current management strategies reported in literature, but simply remind clinicians in a short letter about the main effects of HCQ and that a multidisciplinary approach in managing patients using HCQ should be considered, which include periodic checkups by the ophthalmologist. The following details regarding a list of the adverse events, however, has been added with appropriate citations, as suggested:

"It is yet unclear how HCQ can cause retinal damage. According to studies, the medication impacts the metabolism of retinal cells and binds to melanin in the RPE, which may help to explain why some people continue to experience side effects even after stopping the prescription. With regards to dysfunction related to toxicity, it is thought that HCQ binds to melanin in the RPE, blocking its function, which can lead to irreversible photoreceptor loss and resulting visual field defects over the afflicted sector of the retina. In some cases, Bull's eye configuration can be seen as a ring scotoma on a visual field test when RPE malfunction leading to atrophy occurs across the perifoveal ring when the central fovea is spared. The half-life of HCQ is about 1 month, which a washout period of about 6 months. Early diagnosis of HCQ retinal toxicity is crucial to prevent maculopathy from progressing after HCQ use is stopped.[20] Besides retinopathy, the other ocular side effects, which tend to be benign or infrequent with low doses of HCQ include keratopathy, corneal deposits, punctate/linear corneal opacities, infiltrates, ciliary body deposits, ocular muscular imbalance, lens opacities, papilledema, etc. [21]"

The valuable comments and assistance with the manuscript are greatly appreciated. I look

forward to your final decision regarding our modifications, with the hopes that all concerns have been addressed appropriately.

Revision reviewer

I think this article has no serious problem

Thanks for your comments.

Kind regards,

Marco Zeppieri