Response to: 'Correspondence on '*Festina lente*: hydroxychloroquine, COVID-19and the role of the rheumatologist' by Graef *et al*' by Lo *et al*

We appreciate the interest of Lo *et al* in our opinion piece and thank them for the data presented in their letter.[1 2] Several reports of QT prolongation and torsades de pointes in patients with COVID-19 receiving antimalarials have been published.[3–5] These and other reports have indirectly raised questions regarding the arrhythmogenic potential of hydroxychloroquine (HCQ) when used to treat rheumatic disease.

Lo *et al* used the unique resource of the National Health Insurance Research Database of Taiwan. Through propensity scores, they matched patients who used HCQ and who did not use HCQ for the treatment of newly diagnosed rheumatoid arthritis (RA). Data about other disease-modifying antirheumatic drugs used by the patients was not reported. Therefore, it is unclear if the groups were similar in their RA disease severity, although they seemed similar related to comorbidities. The authors did not find differences in the cumulative risk of arrhythmia between the two groups after 1 year of follow-up. However, a prior meta-analysis on reported cardiotoxic events of antimalarials found that cardiac conduction abnormalities were the most common cardiac adverse events and were associated with higher cumulative doses (median cumulative HCQ dose of 1235 g, median treatment duration 8 years).[6]

The observations from Lo *et al* in the patients with RA are in alignment with the recent preliminary report of a trial regarding the effect of HCQ on hospitalised patients with COVID-19, which did not show any excess of arrhythmias in the HCQ arm after a 1600 mg load followed by 400 mg every 12 hours thereafter.[7] Of note, data regarding incidence of major cardiac arrhythmia was added after the trial launched and was therefore collected in approximately 40% of patients.

Similarly, a recently published of HCQ for COVID-19 showed a very low incidence of arrhythmias but did observe that up to 14.7% of those patients receiving HCQ had a QTc interval greater than 480 ms.[8] This is consistent with several observational studies described in our previous replies where clinically meaningful QTc prolongation occurred more frequently in hospitalised patients with COVID-19 treated with HCQ and azithromycin compared with either drug as monotherapy.[9–11] Risk of QTc prolongation and arrhythmias appear to be most prominent in patients requiring hospitalisation for COVID-19 though cardiac adverse events were not directly monitored in several recent randomised control trials in outpatient populations where HCQ was used for treatment or post exposure prophylaxis.[12–14]

It is important to consider several differences between the use of HCQ for the treatment of COVID-19 compared with its use in rheumatic diseases. HCQ treatment duration in COVID-19 has varied by protocol but lasts for several days. In contrast, patients with rheumatic diseases often are prescribed HCQ for years or even decades. This is relevant since HCQ has a long half-life and may take months to reach steady state concentrations.[15 16] Although a variety of dosing regimens for COVID-19 have been trialled, patients with COVID-19 tend to receive much higher daily doses than the current highest prescribed dose in rheumatology of 400 mg/day.

A recent study of the Veterans Affairs hospitals in the USA of patients using HCQ for prolonged periods of time, the majority of which had systemic lupus erythematosus (SLE), identified that close to 10% of the patients had a QTc of more than 470 ms.[17] Those with prolonged QTc had chronic kidney disease or pre-existent cardiac conditions such as congestive heart failure. Long-term HCQ users who had a prolonged QTc had greater mortality in the univariable analysis but not after adjustment for age, sex and comorbidities.

The COVID-19 pandemic has brought HCQ to the centre stage. As evidence expands, we are learning that HCQ is not an effective treatment for COVID-19, but the spotlight on this old drug has brought new concerns. The lack of association between HCQ use and incident arrhythmias in newly diagnosed the patients with RA in this study by Lo *et al* is reassuring. However, the prolonged QTc observed in other studies and in particular those with chronic kidney disease, a common comorbidity in SLE, and the potential interaction of HCQ with other QT prolonging agents are thought provoking, of clinical relevance and certainly further research is warranted.

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