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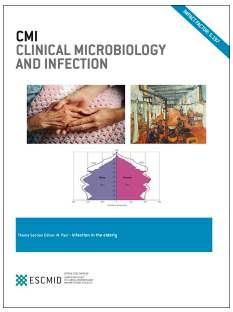

Re: Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients' by Fiolet et al

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Re: Effect of hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients' by Fiolet et al.

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We read with interest the systematic review and meta-analysis by Fiolet et al. [1]

The findings from the systematic review and meta-analysis where hydroxychloroquine, when combined with azithromycin, increased the risk of death, has attracted the most of our attention. The findings between observational studies and randomized controlled trial were in contrast; while pooled analysis of observational studies reported an increased risk of mortality, the only randomized controlled trial included in the review reported no difference in the risk of mortality, with the use of the combination of hydroxychloroquine and azithromycin, compared to non-use of the combination drugs.

The use of azithromycin could lead to prolongation of the QTc interval, the fact which has also been recognized by the authors. However, the potential for azithromycin to prolong QTc interval may not be the main mechanism leading to increased death seen in patients receiving azithromycin. This is owing to the fact that not every form of QT prolongation leads to cardiac arrhythmia or more specifically, torsades de pointes. Although azithromycin leads to small prolongation of the QTc interval, we believe such prolongation does not increase the risk of arrhythmia since azithromycin prolongs the action potential instead of prolonging repolarization which causes torsades de pointes [2].

Whether the use of azithromycin leads to increased risk of death has been an area of dispute even before the COVID-19 pandemic. Similar to the findings reported in the analyses by the authors, there has been discordance in the findings between real-world observational studies and randomized controlled trials in the settings of clinical trials. The largest observational study thus far with analysis of more than 1 million azithromycin exposures reported that exposure to azithromycin significantly increased the hazard of all-cause mortality (hazard ratio = 2.00; 95% confidence interval: 1.51-2.63) and cardiovascular death (hazard ratio = 1.82; 95% confidence interval: 1.23-2.67), with no increased hazard of sudden cardiac death (hazard ratio = 1.59; 95% confidence interval 0.90-2.81) [3]. On the other hand, a 2014 meta-analysis of 12 randomized controlled trials with 15,588 patients, of which few trials evaluated long-term use of azithromycin (up to one year), reported no increased risk for mortality with the use of azithromycin compared to placebo (risk ratio = 0.877; 95% confidence interval: 0.75-1.02) [4].

The reason behind such discordance is unclear, but it may be due to more intense monitoring of patients for cardiovascular toxicity in the settings of clinical trials, compared to day-to-day clinical practice, among patients who receive azithromycin. Nonetheless, experimental mice models have discovered the potential for azithromycin to induce a novel proarrhythmic syndrome characterized

by rapid, polymorphic ventricular tachycardia in the absence of QTc prolongation, due to intracellular loading of sodium ions with subsequent potentiation of sodium current in the cardiac cells and dysregulation of cardiac calcium homeostasis (similar to digoxin therapy) [5]. The finding warrants further exploration, but in the meantime, perhaps azithromycin should be administered with caution in patients with underlying cardiovascular disease, preferable with intense cardiovascular monitoring, resembling those of clinical trials. This includes patients with COVID-19 *per se* since COVID-19 could also lead to myocardial injury.

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