Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Reply to Alizazgar J. Dangers of the use of hydroxychloroquine and azithromycin combination in COVID-19 patients

Dear Editor,

In his recent letter Javad Alizazgar questioned the cardiotoxicity of hydroxychloroquine in combination with azithromycin against COVID-19 [1]. Hydroxychloroquine and chloroquine have remained in clinical use for more than a half-century as an effective therapy for treatment of some malarias, lupus, and rheumatoid arthritis. Data show inhibition of iKr and resultant mild QT prolongation associated with both agents. However, despite these suggestive findings, several hundred million courses of chloroquine have been used worldwide making it one of the most widely used drugs in history, without reports of arrhythmic death under World Health Organization surveillance [2].

The effect azithromycin on QT prolongation was evaluated in healthy people [3]. The participants including 31 female and 16 male aged 19–77 years received azithromycin 500 mg twice daily on day 1 followed by 500 mg/day for 4 days, without using other medications. Electrocardiography (ECG) were performed before and after the initiation of azithromycin. Azithromycin administration was associated with mild prolongation of the QT interval on treatment for 7 days (412.5 ms) and 14 days (419 ms), compared to the previously recorded QT interval (406 ms). Importantly, the proportion of participants with QT intervals greater than the upper normal value of 440 ms was reported same before and after the azithromycin treatment.

The safety of chloroquine plus azithromycin was evaluated and is provided by Pfizer for Zithromax® (https://www.pfizermedicalinformation.com/en-us/zithromax/clinical-pharmacology). Indeed, a randomized, placebo-controlled clinical trial was conducted in 116 healthy subjects who received either chloroquine 1000 mg alone or chloroquine with the coadministration of azithromycin (500, 1000 or 1500 mg). Compared to chloroquine alone, chloroquine in combination with azithromycin was associated with a dose-dependent QT prolongation. The maximal mean prolongation with the coadministration of azithromycin 500, 1000 and 1500 mg was 5 ms (95% upper CI: 10 ms), 7 ms (95% upper CI: 12 ms) and 9 ms (95% upper CI: 14 ms), respectively, which appear mild but of course significant and of the same order as for azithromycin alone [3].

Importantly, not all QT prolongation have the same meaning and consequences. Rather than prolonging repolarization as others macrolides (a pattern which tends to cause *torsade de pointes*), azithromycin prolongs the action potential itself. Alternans (action potential duration alternations) is a measure of cardiac instability in humans and animals associated with the onset of ventricular fibrillation. Due to arrhythmia potential risk from observed QT prolongation, alternans was assessed in the anesthetized guinea pig after azithromycin or chloroquine alone and after combination treatment at clinically relevant concentrations proposed for the management of malaria. Chloroquine alone, but not azithromycin, caused an increase in action potential duration but with only minimal effects on alternans (approximately 10 ms). Azithromycin alone and in combination with chloroquine showed no increase in alternans beyond vehicle baseline responses indicating no additional arrhythmia liability [4]. The inability of azithromycin to cause *torsade de pointes* has been confirmed in two other studies using a dog model, even with high doses of azithromycin [5,6].

In conclusion, azithromycin does prolong the QT interval, which is typically misinterpreted to be a sign of increased risk of arrhythmia/torsade de pointe. In our clinical experience of more than 6000 COVID-19 patients treated with the hydroxychloroquine plus azithromycin, no cases of torsade de pointe or sudden death were observed so far, including in patients aged more than 65 years.

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