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Letter to the Editor

Timing and dosage may be the key in the realisation of hydroxychloroquine + azithromycin treatment benefit in Covid-19 elderly patients

Editor: Dr Jim Gray

Dear Editor,

We read with keen interest the article by Ly et al. titled 'Pattern of SARS-CoV-2 infection among dependant elderly residents living in retirement homes in Marseille, France, March–June 2020' published in the *International Journal of Antimicrobial Agents* [1].

We do not dispute the conclusion of the study, which, despite some limitations, showed a 50% reduction in mortality in COVID-19 patients treated with hydroxychloroquine (HCQ) + azithromycin (AZI) for at least 3 days as part of a well-defined treatment strategy.

However, we believe that it would have been preferable if the authors had insisted on treatment being delivered earlier, long before the stage when mechanical ventilation was needed, and that they had strictly defined the HCQ and AZI dosages. We believe that they could have addressed this by conducting a short comparison in their discussion with other retrospective studies conducted in an institutionally followed group of patients, such as in the retrospective study by Magagnoli et al., which was conducted on US veterans [2]. In that particular study, where all patients were hospitalised, the HCQ + AZI adjusted Hazard Ratio (HR) was 1.31 (95% CI 0.80–2.15; $P = 0.28$) compared with standard of care (SOC), with no distinction of whether the patients had received treatment before mechanical ventilation or not. However, raw data indicated a mortality of 19.2%, 16.2% and 23.4% in the HCQ, HCQ + AZI and no-HCQ groups, respectively, in patients who received HCQ treatment before mechanical ventilation ($P = 0.28$), indicating a possible benefit of HCQ and HCQ + AZI. Of note, the HCQ and HCQ + AZI groups had more patients with elevated hepatic enzymes and inflammatory markers, as well as higher percentages of oxygen saturation < 94%, indicating an aggravated disease condition that was in principle adjusted for using the propensity score method; it is not clearly indicated how disease severity was adjusted for. After adjustment, the length of hospital stay (presumably before discharge or death, but this was not specified) was 33% ($P = 0.01$) longer in the HCQ group and 38% ($P = 0.004$) longer in the HCQ + AZI group. However, when interpreting these data it needs to be borne in mind that on the one hand, if fewer patients died the mean stay may have increased, whereas on the other hand, if fewer patients recovered the mean stay may have increased as well. Moreover, the differences may also indicate that more severely affected patients were allocated to treatments and that adjustment was not properly carried out.

Contrary to the study by Magagnoli et al., the retirement-home patients in the study by Ly et al. were not hospitalised and therefore received earlier treatment at the beginning of the viral infection phase, which is consistent with better treatment efficacy. The treatment was well established (HCQ 200 mg three times daily for 10 days and AZI 500 mg on day 1 followed by 250 mg daily for the next 4 days for at least 3 days) and patients were monitored for potential cardiac side-effects.

Analysis of the study by Magagnoli et al. reveals that the treatment benefit was statistically masked by the heterogeneity of treatment initiation (sometimes initiated after mechanical ventilation was started) and by an uncontrolled dosage of HCQ and HCQ + AZI left to the discretion of the physician. The median dose of HCQ/day was 400 mg and 25% of the treated patients received > 480 mg/day. The maximum dose was not disclosed, but the article by Magagnoli indirectly suggested overdosing with HCQ. Ly et al. could have pointed out that these issues constituted marked bias in the adjusted HR calculated in the study by Magagnoli, which was later regrettably included in the meta-analysis by Fiolet et al., which pointed to the inefficacy and toxicity of HCQ + AZI [3].

Further evidence of the need to administer an appropriate dosage stems from the trial by Borba et al. [4] (which delivered the highest dosage and reported 16 toxic deaths in 41 patients) and the large multi-centre UK Recovery trial [5], which administered the second highest dosage (4 g of HCQ in the first 3 days) and reported a relative increased mortality of 9% in the HCQ arm compared with SOC.

In vitro studies have shown that the effect of HCQ is mainly mediated by alkalinisation of the phagolysosome, where it can concentrate thousands times more than in plasma. This effect can be obtained with low doses of HCQ, due to its long elimination half-life (30–50 days). Small doses may be more adequate in achieving antiviral action. Indeed, due to the high concentration of HCQ in the endosomes, the antiviral effect could be achieved using small or moderate (and non-toxic) doses [6]. High doses of HCQ may be toxic at an early stage (before the cytokine storm) or even deleterious due to HCQ anti-interferon action (via inhibition of TLR7/9 activators of the plasmacytoid dendritic cells (pDCs) to produce massive quantities of type I IFN) [7]. However, overproduction of cytokines may result in more severe forms of the disease [8]. Interferon deficiency may thus predispose to severe forms, which could also explain the negative results of the Recovery study and conversely the positive results by Ly et al.

Indeed, anti-viral therapy is of interest only during the early viral and intermediate phases when the virus is present and replicating, and is of no use during the late inflammatory phase (cytokine storm). Most therapeutic trials have been carried out on hospitalised patients (i.e. probably often too late, as the patients are in the early inflammatory phase).

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Assuming that treatment has to be given early strengthens the results by Ly et al. The authors pointed out that it is not always easy to detect the appearance of symptoms in elderly patients. Patients diagnosed on a case-by-case basis and already presenting with symptoms had a higher chance of dying (40.6%) compared with those diagnosed 'systematically' (16.9%) by PCR.

The study by Ly et al. showed a clear benefit of HCQ plus AZI treatment in particularly vulnerable and frail patients. Given the circumstances, this treatment should be urgently proposed as the primary endpoint in a prospective observational study. Furthermore, given the safety of HCQ when its administration is properly monitored and its likely benefit at moderate doses, the question of medically supervised prophylactic low-dose treatment might also be considered.

Declarations

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