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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Letter to the Editor

Response to the use of hydroxychloroquine in combination with azithromycin for patients with COVID-19 is not supported by recent literature. ☆

We agree with colleagues that excluding six patients from our analysis may have biased the results [1]. We reanalyzed our data following the intention-to-treat concept (Table 1). Patients who died; patients who were transferred to intensive care unit (ICU) and patients who stopped treatment, were included. We also assessed the clinical efficacy of the treatment based on several outcomes including need for oxygen therapy, transfer to ICU and death. The need for oxygen therapy, transfer to ICU and death did not significantly differ between patients who received hydroxychloroquine (HCQ) with or without azithromycin (AZ) and in controls with standard care only. We also calculated the length of hospital stay, which appeared to be significantly shorter in patients treated with HCQ alone, or HCQ and AZ, than in controls (Table 1). Finally, viral persistence was significantly shorter in treated patients, compared to controls when considering the 38 patients with available information. For more details on the characteristics of the 42 patients evaluated in this revised analysis, see our response to IJAA-D-20-00452 [2].

With regard to QT interval prolongation, we have taken great care to avoid HCQ-AZ in patients with cardiac diseases, abnormal EKG, dyskalemia or the routine use of other interacting medications. In addition, close serum electrolyte analysis monitoring was performed in patients with low serum potassium levels at baseline and an electrocardiogram was routinely performed 48 hours after the start of treatment. For more details on our protocol, see our response to letter IJAA-D-20-00373 [3]. Since this preliminary work was done, we have investigated 3,119 patients who received HCQ-AZ for at least three days. QTc prolongation (>60 ms) was observed in 25 patients (0.67%) resulting in discontinuation of treatment in 12 cases, including three cases with QTc> 500 ms. No cases of torsade de pointe or sudden death were observed [4]. Comparing the clinical outcomes of these 3,119 patients to 618 patients who received other regimen or only standard care, HCQ-AZ treatment was associated with a decreased risk of transfer to ICU or death (Hazard ratio (HR) 0.18 0.11–0.27), decreased risk of hospitalization ≥10 days (odds ratios 95% CI 0.38 0.27–0.54) and shorter duration of viral shedding (time to negative PCR: HR 1.29 1.17–1.42) [4].

We sought to find out whether the authors' statement "The use of HCQ in combination with AZ in patients with COVID-19 is not supported by the recent literature" is verified. To this end, we have updated our meta-analysis [5] on the literature data on HCQ and mortality. Methods, excluded studies, reasons for exclusion and data extracted from included studies are detailed in the Supplementary data. In particular, we have included a very recent study with 2019 patients from 17 Spanish private hospitals (see Ayerbe, Intern Emerg Med, 2020 in the Supplementary data). Overall, out of 50,674 patients included from several countries, HCQ was associated with a very significant decrease in the risk of mortality (OR 0.77, 95% confidence interval (CI) 0.71-0.84) and this effect was even greater when only clinical studies were included (OR 0.56, 95%CI 0.48-0.65, Figure 1). In light of the most recent literature review, the statement "The use of HCQ in combination with AZM in patients with COVID-19 is not supported by the recent literature" is not true.

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The authors declare no competing interests.

Ethical approval

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106241.

References

[1] Goldman JD, Diaz G, Urba WJ. Use of hydroxychloroquine in combination with azithromycin for patients with COVID-19 is not supported by recent literature. Int J. Antimicrob Agents 2021;57(1):106174.
[2] Gautret P, Hoang VT, Lagier J-C, Raoult D. Effect of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, an update with an intention-to-treat analysis and clinical outcomes. Int J Antimicrob Agents 2021;57(1):106239.
[3] Gautret P, Honoré S, Lagier J-C, Raoult D. Safety profile of hydroxychloroquine and azithromycin combined treatment in COVID-19 patients. Int J Antimicrob Agents 2021;57(1):106236.
[4] Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis Jul-Aug 2020;36:101791.

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Table 1
Characteristics of studied populations

	Total (N = 42)		Control patients (standard care) (N = 18)		Hydroxychloroquine treatment only (N = 16)		Hydroxychloroquine and azithromycin combined treatment (N = 8)		p-value*
	n	%	n	%	n	%	n	%	
Clinical outcomes									
Oxygen therapy	8	19.0	2	11.1	2	12.5	4	50.0	0.07
Transfer to intensive care unit	5	11.9	1	5.6	2	12.5	2	25.0	0.31
Death	2	4.8	0	0	1	6.2	1	12.5	0.32
Length of stay in hospital (N = 38)**									
Mean ± SD	9.8 ± 7.3		12.1 ± 9.6		8.6 ± 5.2		7.1 ± 3.2		0.04***
Min - max	2 - 47		6 - 47		2 - 24		4 - 14		
Negativity of virus by RT-PCR									
Day3 (n = 41)	12	29.3	2	11.1	5	31.2	5	71.4	0.01
Day4 (n = 40)	17	42.5	5	27.8	7	43.8	5	83.3	0.07
Day5 (n = 40)	17	42.5	4	22.2	7	43.8	6	100	0.003
Day6 (n = 40)	17	42.5	3	16.7	8	50.0	6	100	0.001

* One-sided Fisher's exact test
** Length of stay was calculated in 38 of 42 patients because two patients died, one was discharged against medical advice and information was missing for one patient.
*** Kruskal-Wallis test

[5] Million M, Gautret P, Colson P, Roussel Y, Dubourg G, Chabrière E, et al. Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative meta-analysis between the Big data and the real world. New Microbes and New Infections 2020:100709. In Press, Journal Pre-proof https://doi.org/10.1016/j.nmni.2020.100709 .

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