Letter to the Editor

Effectiveness of hydroxychloroquine in COVID-19 disease: A done and dusted deal?

Dear Sir,

Arshad et al. show evidence for reduced mortality in COVID-19 patients taking hydroxychloroquine alone or with azithromycin in an observational study in the USA (Arshad et al., 2020). Data on the effectiveness and toxicity of hydroxychloroquine are controversial (Liu et al., 2020; Devaux et al., 2020; Gautret et al., 2020; Tang et al., 2020; Geleris et al., 2020).

A total of 539 COVID-19 hospitalized patients were included in our cohort in Milan, from February 24 to May 17, 2020, of whom 174 died in hospital (day 14 probability of death: 29.5% – 95%CI: 25.5–34.0). We divided a subset of our cohort into three groups who started treatment a median of 1 day after admission: those receiving hydroxychloroquine alone ($N = 197$), those receiving hydroxycholoroquine + azithromycin ($N = 94$), and those receiving neither (controls) ($N = 92$). Of the latter group, ten started HIV antivirals (boosted-lopinavir or –darunavir), one teicoplanin, twelve immunomodulatory drugs, or corticosteroids, 23 heparin and 46 remained untreated. The percent of death in the three groups was 27%, 23%, and 51%. Mechanical ventilation was used in 4.3% of hydroxychloroquine, 14.2% of hydroxychloroquine + azithromycin, and 26.1% of controls. Unweighted and weighted relative hazards of mortality are shown in Table 1. After adjusting for several key confounders (see table), the use of hydroxycholoroquine + azithromycin was associated with a 66% reduction in risk of death as compared to controls; the analysis also suggested more substantial effectiveness of hydroxychloroquine in patients with less severe COVID-19 disease (PO2/FiO2 > 300, interaction p-value <0.0001). Our results are remarkably similar to those shown by Arshad et al.

Some important weaknesses in Arshad et al.'s analysis have been pointed out (Lee et al., 2020), but not all of these apply to our study. Our propensity scores include some of the potential confounders that were missing in the analysis by Arshad (e.g., calendar day of admission, disease severity, cardiovascular disease (CVD), baseline plasma CRP); second, we have excluded people receiving other drugs which could have biased the effect of hydroxychloroquine when used in combination. Third, although residual confounding is a possibility (e.g., people with CVD were more frequent in control), people in the control group were more likely to undergo mechanical ventilation, which is a conservative bias. These results from two different real-life settings (Italy and USA), conflict with those of two large randomized trials (Horby et al., 2020; World Health Organization, 2020). Although unmeasured confounding remains the most likely explanation for the discrepancies, a robust meta-analysis is still lacking, and we believe that hydroxychloroquine should be further tested in randomised trials. When best to start treatment is also a question that needs to be addressed in ad-hoc randomized studies.

Table 1
Unadjusted and adjusted marginal relative hazards of in-hospital mortality

	Unadjusted HR (95% CI)	p-Value	Adjusted[*][£] HR (95% CI)	p-Value
	All patients			
Control[#] ($n = 92$)	1.00		1.00	
Hydroxychloroquine ($n = 197$)	0.43 (0.28, 0.64)	<0.001	0.66 (0.39, 1.11)	0.118
Hydroxychloroquine + Azithromycin ($n = 94$)	0.36 (0.21, 0.60)	<0.001	0.44 (0.24, 0.82)	0.009
	[&]Baseline PO2/FiO2 0-300			
Control[#] ($n = 41$)	1.00		1.00	
Hydroxychloroquine ($n = 83$)	0.52 (0.31, 0.87)		0.71 (0.37, 1.35)	
Hydroxychloroquine + Azithromycin ($n = 28$)	0.46 (0.23, 0.93)		0.59 (0.26, 1.35)	
				p-Value for interaction <0.001
	[&]Baseline PO2/FiO2 300+			
Control[#] ($n = 33$)	1.00		1.00	
Hydroxychloroquine ($n = 100$)	0.39 (0.15, 0.97)		0.49 (0.15, 1.63)	
Hydroxychloroquine + Azithromycin ($n = 60$)	0.56 (0.21, 1.52)		0.62 (0.19, 1.97)	

[*] Adjusted for age, gender, number of comorbidities, CVD (yes/no), duration of symptoms, date of admission, CRP and censoring using IPW.
[£] The overall estimate was also adjusted for baseline COVID-19 disease severity.
[#] Heparin, immuno-modulatory drugs, HIV antivirals, combinations of these or no drugs at all.
[&] 45 patients missing baseline PO2/FiO2 not included in the stratified analysis.

Declarations of interest

None declared.

Ethical approval

This analysis is part of the study approved by Ethic Committee Area 1, Milan Italy (2020/ST/049 and 2020/ST/049_BIS, 11/03/2020).

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