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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Editorial

COVID-19 and hydroxychloroquine: Is the wonder drug failing?

The absence of an effective treatment against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led clinicians to redirect drugs that are known to be effective for other medical conditions to the treatment of Covid-19. Chloroquine and hydroxychloroquine are widely used in the treatment of malaria and rheumatic diseases, and they have been suggested as effective treatments for Covid-19 on the grounds of both anti-inflammatory and antiviral effects [1–4]. Mounting data suggest that Covid-19 is burdened by a higher risk of arrhythmic events, with important implications for survival [5]. Hydroxychloroquine, with or without a second-generation macrolide, has also been advocated despite limited evidence for its effectiveness and known detrimental effect of prolongation of the QT interval, which could be a mechanism that predisposes to ventricular arrhythmias [6–8].

In the United States, the FDA issued an Emergency Use Authorization on March 30, 2020, that allowed the use of these drugs in patients with Covid-19 who were not enrolled in clinical trials, and to date, they have been used in many thousands of patients with acute Covid-19 around the world.

Although several multicenter randomized controlled trials are underway, there is an urgent clinical need to provide accurate clinical guidance. Also, some countries have stockpiled these drugs, resulting in a shortage of these medications for approved clinical indications [9].

Table 1. summarizes the most important studies published as of May 27th on the use of hydroxychloroquine for treatment of Covid-19 infection.

Mehra and colleagues published in the The Lancet, May 22nd, the largest observational study to date on the effects of chloroquine or hydroxychloroquine, with or without a macrolide, in 96,032 hospitalized patients (mean age 54 years, 46% women) who tested positive for SARS-CoV-2 [10]. Data from this international registry comprising 671 hospitals in six continents were used to compare patients with Covid-19 who received chloroquine (n = 1868), hydroxychloroquine (n = 3016), chloroquine with a macrolide (n = 3783), or hydroxychloroquine with a macrolide (n = 6221) within 48 h of Covid-19 diagnosis, with 81,144 controls who did not receive these drugs. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias. A Cox proportional hazard model, accounting for many confounding variables, showed a significant increase in the risk of in-hospital mortality with the four treatment regimens compared with the control group (hazard ratios [HR] ranging from 1.33 [95%CI 1.22–1.46] to 1.45 [1.37–1.53]). Analyses using propensity score matching by treatment group supported this result and the risk of in-hospital mortality was similar in men and women.

Geleris and colleagues recently published in the New England Journal of Medicine a study including 1376 consecutive patients with SARS-CoV-2 who had been admitted to a New York City medical center between March 7 and April 8, 2020 [11]. Hospital guidance suggested the use of hydroxychloroquine for patients who had a resting oxygen saturation of less than 94% on ambient air. A total of 59% of the patients were treated with hydroxychloroquine, with 60% of those treated with hydroxychloroquine also receiving azithromycin. The authors assessed the association between hydroxychloroquine use and a composite endpoint of intubation or death over a median follow-up of 22.5 days. In the adjusted analyses, there was no evidence of a substantial difference in the rate of the composite endpoint (HR 1.04; 95%CI 0.82–1.32). The findings were confirmed in the sensitivity analyses.

In a retrospective multicenter cohort study, recently published in JAMA, the authors describe the association between use of hydroxychloroquine, with or without azithromycin, and in-hospital mortality among inpatients diagnosed with Covid-19 [12]. A random sample of all admitted patients with laboratory-confirmed Covid-19 in 25 hospitals (representing 88.2% of patients with Covid-19 in the New York metropolitan region) was selected. Among 1438 hospitalized patients with Covid-19 (median age 63 years, 40% female) overall in-hospital mortality was 20.3%. The probability of death was significantly increased for all treatment regimens compared to neither drug (Table 1). Further, in logistic models, compared with patients receiving neither drug, cardiac arrest was significantly more likely in patients receiving hydroxychloroquine + azithromycin, but not hydroxychloroquine alone or azithromycin alone.

In one comparative observational study published in the BMJ by Mahévas and colleagues, survival at 21 days with or without acute respiratory distress syndrome did not differ between the groups treated with hydroxychloroquine (84 patients) versus the control group (89 patients) [13]. The authors concluded that hydroxychloroquine in moderately ill patients with Covid-19 was not useful, and perhaps even harmful.

In another single center, retrospective, observational study published in JAMA Cardiology, that included 90 hospitalized subjects (mean age 60 years, 49% female) receiving hydroxychloroquine (41%) or hydroxychloroquine + azithromycin (59%), it was observed QTc prolongation (ΔQTc 21 ms), and those taking hydroxychloroquine + azithromycin had greater QT prolongation than those taking hydroxychloroquine alone [14].

Following current scientific evidence on potential harm related to the use of hydroxychloroquine or chloroquine alone or in combination with azithromycin for the treatment or prevention of Covid-19, the European Medicines Agency (EMA) and the FDA released, on April 23rd and April 24th, respectively, drug safety announcements. The FDA stated "*we are warning the public that hydroxychloroquine and chloroquine, either alone or combined with azithromycin, when used for Covid-19 should be limited to clinical trial settings or for treating certain hospitalized patients*

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Table 1
Relevant studies published as of May 27th, 2020 on use of hydroxychloroquine for treatment of Covid-19 infection.

Study	Journal	Published Date	Study Population	Treatment Regimen	Outcome
Mercuro et al. [14] Single center, retrospective, observational study	JAMA Cardiology	May 1st, 2020	90 hospitalized subjects, mean age 60 years, 49% female	All patients Received HCQ, and 53 (59%) received HCQ + AZM*	QTc prolongation (ΔQTc 21 ms), and those taking HCQ + AZM had greater QT prolongation than those taking HCQ alone. One patient developed torsades de pointes
Mahévas et al. [13] Comparative observational study	BMJ	May 5th, 2020	173 hospitalized subjects, median age 60 years, 28% female	84 patients received HCQ and 89 did not (control group)**	Rate of survival without transfer to the intensive care unit was not significantly different among those taking HCQ and those who did not (76 vs. 75%)
Geleris et al. [11] Single center, retrospective, observational study	NEJM	May 7th, 2020	1376 hospitalized subjects, 60.5% age ≥ 60 years, 43% female	811 (58.9%) received HCQ*** and 565 did not (control group).	No significant association between HCQ use and the primary outcome of intubation or death (HR 1.04, 95%CI 0.82–1.32). Results were similar in multiple sensitivity analyses.
Rosemberg et al. [12] Multicenter, retrospective, cohort study	JAMA	May 11th, 2020	1438 hospitalized subjects, median age, 63 years, 40.3% female	Four groups: 1) HCQ + AZM (n = 735), 2) HCQ alone (n = 271), 3) AZM alone (n = 211), or 4) neither drug (n = 221)¥	Overall in-hospital mortality rates in the four groups were 25.7% (1), 19.9% (2), 10.0% (3), and 12.7% (4), respectively, with no significant between-group differences after adjustment for potential confounders
Mehra et al. [10] Multinational registry study	The Lancet	May 22nd, 2020	671 hospitals in six continents for a total of 96,032 patients, mean age 53.8 years, 46.3% female	14,888 patients were in the treatment groups: 1868 received CQ, 3783 received CQ + macrolide, 3016 received HCQ, and 6221 received HCQ + macrolide§. 81,144 patients were in the control group	After controlling for multiple confounding factors when compared with mortality in the control group (9.3%); HCQ (18.0%; HR 1.3, 95%CI 1.2–1.5), HCQ + macrolide (23.8%; HR 1.5, 95%CI 1.4–1.5), CQ (16.4%; HR 1.4, 95%CI 1.2–1.5), and CQ + macrolide (22.2%; HR 1.4, 95%CI 1.3–1.5) were each independently associated with an increased risk of in-hospital mortality

Note: HCQ: hydroxychloroquine, AZM: azithromycin, CQ: chloroquine. HR: hazard ratio, CI: confidence interval. Treatment regimens: * HCQ 400 mg twice on day 1, then 400 mg daily on days 2 through 5; ** HCQ 600 mg/day within 48 h of admission; ** HCQ 600 mg twice on day 1, then 400 mg daily for a median of 5 days; ¥ refer to eTable1 of the original publication; § CQ alone, 765 mg for 6.6 days; HCQ alone, 596 mg for 4.2 days; CQ + macrolide, 790 mg for 6.8 days; and HCQ + macrolide, 597 mg for 4.3 days.

under the emergency use authorization ". On the same line, the EMA stated: "*Healthcare professionals should carefully consider the possibility of side effects, particularly with higher doses, and exercise extra caution when combining treatment with other medicines such as azithromycin that may cause similar side effects on the heart*".

In conclusion, we strongly believe that a cardinal principle of practicing medicine is "first, do no harm" and even in situations like Covid-19 where you believe a desperate disease calls for desperate measures, good and responsible physicians should take a step back and ask themselves if they are causing harm. As physicians involved in the frontline of this unprecedented emergency, serving hundreds of patients in a dedicated Covid-Hospital, we share with colleagues around the world the burden and the responsibility of taking hard decisions on daily-basis; however, following the World Health Organization global announcement to temporarily halting any ongoing trial of hydroxychloroquine for treating Coronavirus patients, we believe that evidence-based medicine should always come first even in emergency situations like SARS-CoV-2 pandemics.

Declaration of Competing Interest

None.

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