Early Treatment with Hydroxychloroquine and Azithromycin in 10,429 COVID-19 Outpatients: A Monocentric Retrospective Cohort Study

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ABSTRACT

Objectives We evaluated the age-specific mortality of unselected adult outpatients infected with SARS-CoV-2 treated early in a dedicated COVID-19 day hospital and we assessed whether the use of HCQ+AZ was associated with improved survival in this cohort.

Methods A retrospective monocentric cohort study was conducted in a day hospital of an expert center (Institut Hospitalo-Universitaire Méditerranée Infection) from March to December 2020 in adults with PCR-proven infection who were treated as outpatients with a standardized protocol. The primary endpoint was 6-week mortality, and secondary endpoints were transfer to the intensive care unit and hospitalization rate.

Results Among 10,429 patients (median age, 45 [IQR 32-57] years; 5,597 [53.7%] women), 16 died (0.15%). The median delay from symptoms to day hospital was 4 days [IQR 2-6], and that from a positive PCR test to day hospital was 1 day [1-3]. The infection fatality rate was 0.06% among the 8,315 patients treated with HCQ+AZ. No deaths occurred among the 8,414 patients younger than 60 years. Older age and male sex were associated with a higher risk of death, ICU transfer, and hospitalization. Treatment with HCQ+AZ (0.17 [0.06 – 0.48]) was associated with a lower risk of death, independently of age, sex and epidemic period. Meta-analysis evidenced consistency with 4 previous outpatient studies (32,124 patients – Odds ratio 0.31 [0.20 – 0.47], $I^2 = 0\%$).

Conclusions Early ambulatory treatment of COVID-19 with HCQ+AZ as a standard of care is associated with very low mortality, and HCQ+AZ improve COVID-19 survival compared to other regimens. Zinc and anticoagulants are likely to further improve outcomes. Most COVID-19-associated deaths are preventable with early detection and outpatient treatment.

INTRODUCTION

The SARS-CoV-2 pandemic infected 95 million people and killed 2 million people by January 19, 2021, corresponding to an overall infection fatality rate (IFR) of 2% (1). Health agencies in Western countries have focused on contagion control measures (lockdown), late-stage hospitalized patients, intensive care units, and vaccination, but for reasons that are yet to be clarified, early treatment has not been emphasized (2-4). In eastern countries such as China, India, Iran, and Saudi Arabia, where early treatment and prevention with repurposed antivirals, particularly hydroxychloroquine (HCQ), has been widely implemented (5-8), lower IFRs than Western countries, where early treatment with orally available molecules has been overlooked or even discouraged, have been reported (1). In addition, countries using chloroquine or HCQ as a treatment from the start of the epidemic had a much slower dynamic in daily deaths (9).

The antiviral effect of chloroquine and its derivatives (HCQ) against SARS-CoV-2 was identified as early as February 2020 through in vitro studies in early Chinese publications (10,11) and a preliminary trial in our center (12). The synergistic *in vitro* antiviral effect of the combination of HCQ with azithromycin (AZ) was further reported (13). In addition, HCQ has several anti-inflammatory and antithrombotic properties (14), which is of particular interest in the context of COVID-19-associated inflammation and coagulopathy. Our previous observational study (15) reported a beneficial effect on thousands of cases, but in- and outpatients were not analyzed separately. The largest publicly available ambulatory studies included an Iranian study with 28,759 outpatients and a study in Saudi Arabia with 5,541 outpatients, both evidencing a 4-fold reduced risk of death with HCQ (5,6). The importance of earliness of treatment has also been recently emphasized by a Chinese study reporting that HCQ, when administered in the first 5 days after symptom onset, improves prognosis and reduces viral shedding (7).

The effect of early ambulatory treatment with HCQ combined with AZ on COVID-19 mortality has not been reported in a large series. Here, we evaluated the age-specific mortality of unselected adult outpatients infected with SARS-CoV-2 managed early in a dedicated COVID-19 day hospital offering standardized treatment based on HCQ+AZ. We also assessed whether the use of HCQ+AZ was associated with improved IFR and lower rates of intensive care unit (ICU) admission and hospitalization in a conventional ward (HC) in this cohort. A meta-analysis of studies assessing early HCQ in COVID-19 outpatients was conducted to test consistency with available literature.

METHODS

Study design, setting and participants

This retrospective cohort study, reported according to the STROBE guidelines, was conducted in the day hospital of the Institut Hospitalo-Universitaire (IHU) Méditerranéee Infection (https://www.mediterranee-infection.com/), Assistance Publique-Hôpitaux de Marseille (AP-HM), southern France, with an inclusion period from March 17 to December 31, 2020, and follow-up until February 11, 2021. Compared to previous retrospective cohort studies of our center (15), this study focused on outpatients with ambulatory treatment, namely, patients who presented with nonsevere COVID-19 who returned home and were not immediately hospitalized in a conventional ward. Detailed methods, COVID-19 management and ethics statement are provided in the Supplementary data.

COVID-19 management

Briefly, patients were systematically administered HCQ at 200 mg tid for 10 days, AZ at 500 mg on day 1 and then 250 mg for 4 days in the absence of contraindications. HCQ+AZ was

prescribed as off-label medication. Anticoagulants, indicated only for at-risk patients, and zinc were subsequently added before epidemic period 2.

Outcomes

The primary objective was to evaluate the age-specific 6-week IFR of unselected adult outpatients infected with SARS-CoV-2 who were managed early in a dedicated COVID-19 day hospital offering standardized treatment based on HCQ+AZ. The secondary objective was to test whether the use of HCQ+AZ was associated with improved IFR and lower ICU and HC rates in this cohort. The main considered confounding factors were age, sex, and epidemic period. The comprehensiveness of the HC cases, ICU transfers and deaths was optimized by using an automatic query of the informatic system of the APHM (Departement d'Information Médicale (DIM)) and, for deaths only, the National Register of Deceased Persons (NRDP) accessed on March 2021, which included reported deaths for 2020 and January and February 2021 (16). In agreement, the deaths were collected for all patients regardless of the place of death (in hospital or not) in France.

Statistical analysis

Associations between treatment (HCQ+AZ), age, sex and epidemic period, and clinical outcomes (deaths, ICU admissions, HC) were estimated using multivariable logistic regression with adjustments for age, sex and epidemic period. A two-sided α value of less than 0.05 was considered statistically significant. Analyses were carried out using SAS 9.4 statistical software (SAS Institute, Cary, NC). Meta-analysis on outpatient treatment of COVID-19 with HCQ was performed using random effects modeling for odds ratios. Meta-analysis was performed using the R package meta.

RESULTS

Participants

In 2020, 11,725 COVID-19 patients were treated and followed in our day hospital. Among these, 503 were immediately hospitalized in the conventional ward and were excluded. Among 11,221 outpatients, 792 were excluded for the following reasons: 424 patients with unavailable information on treatment, 265 minor patients, 82 considered cured, and 72 without a positive PCR test (though one patient could have been excluded for more than one reason) (Figure 1). None refused the use of their data. After exclusion of these patients, our ambulatory cohort included 10,429 outpatients.

The trend in the number of patients seen in the day hospital per week is shown in Supplementary Figure 1 and reflects 3 pandemic periods corresponding to different variants (17,18). The median age was 45 [IQR 32-57] years, and 5,597 [53.7%] were women. Age and the sex ratio differed according to the epidemic period (Supplementary Table 1 & Supplementary Figure 2), with patients being older during the third period. The median delay from symptom onset to day hospital attendance was 4 days (interquartile range 2 to 6 days, information available for 1,066 symptomatic patients seen in December 2020), and that from the screening positive test was 1 day (1-3 days, information available for 1,119 patients). These delays were very similar among all age intervals (Supplementary Table 2).

Among the 10,429 included patients, 8,315 received the combination therapy HCQ+AZ (79.7%), 1,091 received AZ alone (10.5%), 207 received HCQ alone (2.0% - mainly the first week, Supplementary Figure 1), and 816 did not receive either HCQ or AZ (7.8%). The reasons for not prescribing treatment are mentioned in Supplementary Table 3. No serious adverse events nor *torsade de pointes* was observed. Of these 10,429 patients, 21 had a second SARS-CoV-2 infection (0.2%) with a median time to reinfection of 160 days (interquartile range 127 to 209 days).

Outcomes

Deaths

Among the 10,429 ambulatory patients, there were 16 deaths (0.15%) (Table 1, Figure 2 & Supplementary Figure 1). No patient under 60 years of age died (0/8414 (0%), 95% confidence interval 0.0% to 0.4%) (Figure 2). Therefore, the IFR among the 2,015 patients aged 60 and over was 0.8%. 11/16 deaths (70%) were common to both data sources (DIM & NRDP). Two were identified only with the DIM, and three were identified only with the NRDP. The median age of the decedents was 78 years (interquartile age 69 – 82 years), and 12/16 (75%) were male. Thirteen (81%) had a Charlson score ≥ 5, corresponding to a risk of death within one year of more than 85%, so that only three were expected not to die in the following year. Among 13 patients with a known cause of death, 12 presented with respiratory failure, 1 presented with anaphylactic and septic shock after dexamethasone, one presented with neurological failure, and 6 presented with severe coagulopathy. None of the deaths with a known cause were related to a side effect of hydroxychloroquine and/or azithromycin or a *torsade de pointe*.

There were 5 deaths among the 8,315 patients who received HCQ+AZ (0.6 on 1000 patients) and 11 among the 2,114 who received other treatments ($p < 0.0001$). There were 9 deaths among the 1,091 patients who received AZ alone (0.82%) and 2 deaths among those who received no treatment. In the multivariable logistic regression, age, sex, and treatment, but not epidemic period, were associated with a significant difference in the risk of death (Table 2). HCQ+AZ was associated with a significant 83% decrease in the risk of death (0.17, 0.06 - 0.48) independent of age, sex or epidemic period.

Intensive care unit admissions

Only 24 patients were transferred to the intensive care unit (0.23%), with no patient under 40 years of age being transferred (Supplementary Table 4). In the multivariable logistic regression, age and sex were associated with ICU transfer (Supplementary Table 5). Period 3 was associated with a nonsignificant (aOR 0.44, 0.19 – 1.02) 66% decrease in the risk of being transferred to the ICU independent of age, sex or HCQ+AZ treatment. HCQ+AZ was associated with a 44% nonsignificant (0.56, 0.24 – 1.30) decrease in the risk of ICU transfer (Supplementary Table 5).

Hospitalizations

Two hundred and seventy-eight patients (2.7%) were subsequently hospitalized (Supplementary Table 6). In the multivariable logistic regression, age, sex, and epidemic period, but not HCQ+AZ, were associated with the hospitalization rate. The hospitalization rate was decreased by 30-35% for periods 2 and 3 compared with period 1 (Supplementary Table 7).

DISCUSSION

Here, we demonstrated the feasibility and efficacy of early outpatient management with a combination HCQ+AZ treatment to prevent COVID-19-related death. In our cohort, as in the largest published ambulatory series (Table 3 and ref. 5,6), treatment with HCQ was not associated with serious cardiac side effects but was associated with a significant IFR decrease of 75%. The present cohort is among the largest cohorts of COVID-19 patients treated in the outpatient setting, with the lowest mortality rates: the IFR was 0.15% (0.06% among those treated with HCQ+AZ) versus 0.7% and 1.1% (0.30% and 0.39% among HCQ-treated patients) in the Iranian (169/22,784 patients with positive PCR) and Saudi ambulatory cohorts

(61/5,541 patients), respectively (Table 3 and ref. 5,6). In France, a prospective cohort study reported a 0.1% IFR among 43,103 outpatients monitored with a telesurveillance solution (19), however PCR confirmation was not systematic, treatment was not analyzed and National Register of Deceased Persons was not used, limiting the interpretation of these results.

In our cohort, the IFR among patients of all ages treated with HCQ+AZ was 60 per 100,000, which is much lower than the natural infection rate, even when evaluated under the best conditions, as in Iceland, where it was estimated to be 300 per 100,000 (20). The IFR was also estimated to be 89 per 100,000 in patients who were < 70 years of age in Denmark (21). For the same age range in our cohort, the IFR was 41 per 100,000 (4/9,700) for all ambulatory patients and 25 per 100,000 for those treated with HCQ+AZ (2/7,823) (see Table 1).

The cardiotoxicity of HCQ, previously considered irrelevant to oral administration and usual doses (22), has been exaggerated by studies with a potential conflict of interest, notably in the retracted article published in the Lancet (23). White (22) showed that the concentrations needed to inhibit the hERG channel responsible for QT prolongation were 4 to 14 times higher than the concentrations observed in plasma at usual doses. In our center, we developed a smartwatch electrocardiogram and artificial intelligence for assessing the cardiac rhythm safety of HCQ-AZ and did not find any QTc prolongation (24). As shown in our cohort, a simple clinical and biological evaluation with blood potassium assessment and the use of a first electrocardiogram allowed us to initiate treatment with acceptable safety in terms of potential arrhythmias.

The Figure 3 shows, in a meta-analysis, that all the studies carried out on outpatients, with minimal quality criteria (biological diagnosis, representative population with adequate control and at least 1 death), are all in the same direction (Supplementary Table 8 & Supplementary Table 9). All these studies reported a similar magnitude (3-fold decrease in the risk of death), and showed that early treatment of COVID-19 with hydroxychloroquine

improve survival in COVID-19 (n = 32,124 patients in 5 countries, Odds ratio 0.31 [0.20 – 0.47]) without heterogeneity (I^2 = 0%). These results remained unchanged when excluding one study not controlling the role of age (Supplementary Figure 3). All RCTs were excluded because of lack of systematic biological diagnosis or absence of death (Supplementary Table 9). However, new RCTs with medical quality criteria are not expected to change results since it has been shown that results from RCT and observational studies did not differ significantly (25,26). Interestingly, early administration of fluvoxamine was found to prevent clinical deterioration in outpatients (27). Strikingly, both fluvoxamine and HCQ interfere with the interaction between the host sigma-2 receptor and the viral ORF9c protein, critical for enabling immune evasion and to coordinate cellular changes essential for the SARS-CoV-2 life cycle.

The main limitation of the present cohort is its lack of assessment of comorbidities. However, consistency with similar studies controlling for co-morbidities was evidenced by meta-analysis. All outpatients reported here were considered nonsevere by the day-hospital physician based on routine assessment of saturation and dyspnea, but data on accurate initial clinical assessment was not collected. Follow-up was not systematically proposed after May 2020, so hospitalizations in and transfers to critical care units outside our city hospitals (APHM) may have been overlooked. However, deaths were identified through the French national register, thereby controlling this bias. The strengths of our study include the large sample size, the homogeneous management of patients associated with the monocentric design, and the double collection of death data by means of two registers: a local (city public hospital system) and national (French National Register of Deceased Persons) register.

Finally, there are old and nontoxic drugs with in vitro and preliminary clinical efficacy on SARS-CoV-2 infection, such as HCQ, ivermectin (28), or fluvoxamine (27). Such drugs may be neglected when political factors, massive funding and fear lead to irrational decisions

(29). It seems urgent that governments and health authorities take in hand the evaluation of nonprofitable drugs, which are probably more effective than the drugs developed for this pandemic. This requires a profound paradigm shift, the extent of which was revealed by COVID-19 and which would be in line with the reflections on Tamiflu, recently documented in the British Medical Journal (29). As long as the planned obsolescence of drugs, the current standard in Western countries, is not challenged, these richest countries and, theoretically, the most scientifically advanced, will remain those with the highest COVID-19 fatality rate in the world.

ARTICLE INFORMATION

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Declaration of competing interest

The authors declare no competing interests. Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and

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Table 1. Death rate according to treatment and age and comparison with the Diamond Princess cruise

	All			*HCQ-AZ*			*Other treatments*			*Diamond Princess*	
	n	***%***	***p-value***	***n***	***%***	***p-value***	***n***	***%***	***p-value***	***n***	***%***
n	16/10,429[#]	0.15	***	5/8,315	0.06	***	11/2,114	0.52	***	7/613	1.14
Male sex	4,832/10,429	46.33		3,914/8,315	47.07		918/2,114	43.42		-	-
Age interval (years)											
18-29	0/2,157	0.00		0/1,752	0.00		0/405	0.00		0/28	0.00
30-39	0/2,004	0.00		0/1,650	0.00		0/354	0.00		0/34	0.00
40-49	0/2,074	0.00		0/1,692	0.00		0/382	0.00		0/27	0.00
50-59	0/2,179	0.00		0/1,726	0.00		0/453	0.00		0/59	0.00
>59	16/2,015	0.79	**	5/1495	0.33	***	11/520	2.21	ns	7/465	1.51
60-69	4/1,286	0.31		2/1,003	0.20		2/283	0.71		0/177	0.00
70-79	6/555	1.08		1/395	0.25		5/160	3.13		3/234	1.28
80-89	6/158	3.80		2/93	2.15		4/65	6.15		4/54	7.40
>89	0/16	0.00		0/4	0.00		0/12	0.00		-	-

[#]An additional death occurred that was unrelated to COVID-19 or treatment but was not included in the analyses because no information can be described for forensic reasons. HCQ: hydroxychloroquine, AZ: azithromycin. *: p<0.05, **: p<0.01, ***: p<0.001, ns: nonsignificant. Binomial

exact test versus Diamond Princess cruise mortality rates (30). Patients aged over 60 years were grouped for statistical comparisons due to the low number of events in each cell.

Table 2. Effect of HCQ-AZ on outpatient mortality - Multivariable logistic regression (n= 2,015 patients ≥ 60 years)

		OR	95% CI	p
Age (ref. 60-69 years)	70-79	2.81	0.88 – 8.96	0.0802
	>79	8.29	2.52 – 27.20	0.0005
Sex (ref. women)	Men	3.61	1.29 - 10.07	0.0145
Epidemic period (ref. period 1)	Period 2	0.14	0.01-2.58	0.1856
	Period 3	0.58	0.17 – 1.93	0.3743
Treatment (ref. no dual therapy)	HCQ+AZ	0.17	0.06 - 0.48	0.0007

OR: odds ratio, CI: confidence interval, Ref: reference, AZ: azithromycin, HCQ: hydroxychloroquine. The two-way interaction between treatment and age was not statistically significant (p = 0.57).

Table 3. Clinical studies on ambulatory treatment of COVID-19

Study	Country	Specific population	Treatment	Sample size	Effect on mortality	Overall mortality/1000
Mokhtari, Int Immunopharmacol, 2021	Iran	Community	HCQ	22,784[a]	Significant decreased mortality	7.0
Present Study	France	Community	HCQ+AZ	10,429	Significant decreased mortality	1.5
Sulaiman, MedRxiv, 2020	Saudi Arabia	Community	HCQ	5,541	Significant decreased mortality	11.0
Ip, BMC Infect Dis, 2021	USA	Community	HCQ	1,274	Nonsignificantly decreased mortality	40.0
Szente Fonseca, TMAID, 2020	Brazil	Community	HCQ	717	Nonsignificantly decreased mortality	15.3
Seftel, Open Forum Infect Dis, 2021	USA	Community	Fluvoxamine	113	Nonsignificantly decreased mortality	8.8
Guerin, Asian J Med Health, 2020	France	Community	HCQ+AZ	80	Nonsignificantly decreased mortality	11.4

[a]After exclusion of patients without a positive PCR test. HCQ: hydroxychloroquine, AZ: azithromycin. No randomized controlled trial with PCR-proven diagnosis and at least 1 death was identified in the outpatient setting, probably because the sample size needed to identify a significant difference with sufficient power in mortality risk is difficult to achieve with such a design in this context. Excluded studies (no death, absence of systematic PCR diagnosis) are listed in Supplementary Table 8.

Figure legends

Figure 1. Study flowchart

[a]One patient may be excluded for more than one reason. IHU: Institut Hospitalo-Universitaire Méditerranée Infection, HCQ: hydroxychloroquine, AZ: azithromycin.

Figure 2. Infection fatality rate by age class

HCQ-AZ: hydroxychloroquine and azithromycin treatment. There were only 16 patients > 89 years, with no deaths in this cohort.

Figure 3. Meta-analysis on studies using HCQ for COVID-19 in outpatients

Meta-analysis was performed using random effects modeling for odds ratios (OR). Chi square based Q test and I^2 statistic were used to evaluate the statistical heterogeneity between the studies. Meta-analysis was performed with using the R package meta.