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Beneficial Effect of the Hydroxychloroquine or Chloroquine/Azithromycin Combination in Patients with COVID-19: Results of an Observational Study

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Abstract **Original Research Article**

One hundred and three patients with COVID-19 received chloroquine or hydroxychloroquine/ azithromycin combination between March 24 and May 26, 2020. The dosages of hydroxychloroquine and azithromycin were in accordance with the protocol of the Moroccan Ministry of Health. The mean age of our series was 43.7 ± 16 years, and males were the most affected (55%). 19 patients had comorbidities, dominated by arterial hypertension (10.7%), diabetes (7.8%), and pulmonary pathologies (4.9%). Seventy-seven patients were asymptomatic (74.8%). Dry cough was the main functional symptom in our series (55.3%). The most predominant scan appearance was isolated ground glass areas. The majority of patients in our series (52%) were under chloroquine/azithromycin, while 43% of patients were under hydrochloroquine/azithromycin, all patients benefited from adjuvant treatment with vitamin C & D and Zinc. During the treatment period, 39 patients representing 38.6% of the cases showed side effects of the treatment, with an average delay of 4.6 days, the most common side effects were: gastrointestinal affections in 21.4% of the cases, hepatobiliary affections in 12.6% of the cases. Nine people died (8.8%). All other patients who received the HCQ/AZT combination were considered cured in 37.6% of cases only at D 9, with a mean hospitalization time of 17 days (10-40 days).

Keywords: Azithromycin, COVID-19, Nursing home, Hydroxychloroquine, Secondary Effects.

INTRODUCTION

The coronavirus family is responsible for respiratory infections in mammals and birds. They are RNA viruses, grouped into four subfamilies: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. In humans, four of these viruses are responsible for mild disease in immunocompetent patients (HCoV-229E, HCoV-OC43, HCoV-NL63 and HKU1) [1]. Two are responsible for severe and life-threatening pathologies: SARS-CoV-1 and MERS-CoV, identified in 2003 and 2012 respectively [1-3].

In December 2019, the appearance of several cases of pneumonitis of unknown origin in Hubei province in China led to the identification in January 2020 of a new coronavirus [4], named SARS-CoV-2 by the Coronavirus Working Group of the International Committee on Virus Taxonomy [5]. It is a Betacoronavirus probably transmitted to humans by pangolin in the Huanan seafood market, located in Wuhan city [6]. Human-to-human transmission led to the spread of the virus to Thailand and then to other countries, causing a pandemic today [7].

SARS-CoV-2 causes sometimes a severe respiratory disease, named "COVID-19" by the World Health Organization (WHO) [8].

In the midst of the COVID-19 pandemic, Professor Raoult's team from the Marseille University Hospital Institute published on March 20 the first results of the SARS-COV2 study, which concluded that the administration of hydrochloroquine and azhytromycin (HCQ + AZ) before the onset of COVID-19 complications is safe and associated with a very low mortality rate in patients [9].

The Ministry of Health, following the recommendations of the technical and scientific committee, has developed a therapeutic protocol on 24/03/2020 based on chloroquine sulfate or hydrochloroquine in combination with azithromycin in the 1st intention, and the combination lopinavir/ritonavir in the 2nd intention [10].

We present the results of an observational study obtained in 103 patients with COVID 19, who received hydrochloroquine or chloroquine and azithromycin in combination.

MATERIALS AND METHODS

Treatments were initiated between March 24, 2020 and May 26, 2020 in all patients with a positive SARS COV2 specific PCR with or without clinical symptoms, or a high risk contact, or contacts with comorbidities.

Patients received the following protocol:

1. Choloroquine (Nivaquine) 500mg*2/d or hydroxy-chloroquine sulfate (plaquinine) 200mg*3/d for 10 days.
2. Azithromycin at a dosage of 500 mg on the first day and then 250 mg on the following 4 days.
3. Adjuvant treatment: Vitamin C, Vitamin D, ZINC, PPI.

Prior to the start of the therapeutic protocol, the patients underwent a minimal check-up in order to detect any contraindications to the treatment: CBC-CRP, hepatic check-up, renal check -up, haemostasis check -up, complete ionogram, glycaemia, ECG.

A monitoring protocol for the HCQ/AZT association has been developed by our pneumology department at the ARRAZI University Hospital, which consists of: twice-daily monitoring, a biological check-up twice a week and at the end of the treatment, and an ECG at D0, D2, and at the end of the treatment.

The patients' comorbidities were investigated, in particular: diabetes, arterial hypertension, heart disease, asthma and COPD, which are important factors in the context of a respiratory viral infection.

All adverse effects of treatment as well as clinical signs suggestive of efficacy or worsening were regularly noted in the medical record.

Concerning the criteria of cure are mainly virological: 2 negative -PCR test at 24D interval at d9, or at d15, or at d21, or at d28.

RESULTS

Among the 103 patients, 97 patients received this treatment after performing the PCR test diagnosed COVID+ and 6 patients were treated preventively even with a negative PCR, because they have a close contact with a case diagnosed COVID+.

The demographic characteristics of the 103 patients treated with the combination are presented in Table I.

The mean age was 43.7 ± 16 years, the most predominant age range was [31 years -50 years]. The male sex was the most affected (55. %).

Nineteen patients had comorbidities, dominated by arterial hypertension (10.7%), diabetes (7.8%), and pulmonary pathologies (4.9%) (Table II).

Seventy-seven patients were asymptomatic (74.8%). Dry cough represents the main functional symptom in our series, it is reported in 55.3% of patients.

Table I: Demographic characteristics of the patients

	Effective	Percentage
Age range		
[10-30 years]	23	22.5%
[31-50 years]	46	45.1%
[51-70 years]	26	25.5%
[71-90 years]	8	7.7%
Gender		
Male	57	55.3%
Female	46	44.7%

Table II: Patients' medical history

	Effective	Percentage
ATCDS		
HTA	11	10.7%
Diabetes	8	8.7%
Pulmonary pathology		
Pleural tuberculosis	2	1.9%
Multifocal tuberculosis	1	1%
Asthma	1	1%
COPD	1	1%
Renal pathology	1	1%
OTHER		
Anemia	1	1%
VIH	1	1%
Hemorrhagic rectocolitis	1	1%

The most common biological abnormalities were: increased ferritinimia in 55.6% of patients, elevated fibrinogen in 47.9%, elevated d-dimer in 45 patients, lymphopenia in 30.4%, and elevated LDH in 17.7% of patients.

ECG was systematically performed in all our patients, it objectified a prolongation of the QT interval in only one patient, and a bradycardia in another. The thoracic CT scan was performed in 30 patients, the most predominant aspect of which was the isolated ground glass areas table III.

Table III: The scan characteristics of the patients

	Effective	Percentage
Normal	5	16.6%
Isolated ground-glass opacities	12	40%
Condensation	1	3.3%
Condensation and ground-glass opacities	11	36.7%
Nodular ground glass	1	3.3%

The majority of the patients in our series (52%) were under chloroquine/azithromycin, when 43% of the patients were under hydrochloroquine/azithromycin, all the patients benefited from an adjuvant treatment based on vitamin C and D, Zinc.

During the treatment period, 39 patients or 38.6% of cases presented side effects of the treatment, with an average delay of appearance of 4 to 6 days. The most common side effects were: gastrointestinal affections in 21.4% of cases, hepatobiliary affections in 12.6% of cases, see Table IV.

Table IV: Side effects of chloroquine/hydrochloroquine

Type of Side Effect	Percentage
Digestive effects (nausea, vomiting).	51.4%
Hepatobiliary effects (disturbance of the liver balance).	12.6%
Ophthalmological effects	7.8%
Psychiatric effects (insomnia)	4.9%
Hematological effects (lymphopenia).	6.8
Nervous system effects (involuntary movement).	1%
Cardiac effects (QT prolongation).	1%

Finally, during the study period, 9 people died among the 103 patients studied, i.e. 8.8% of the cases of the study. These patients were all men, all of whom had comorbidities such as hypertension, diabetes, and COPD. All of these deaths occurred due to severe respiratory complications of the disease. All other patients who received the HCQ/AZT combination were considered cured in 37.6% of cases only at D 9, with a mean hospitalization time of 17 days (10-40 days) Table V.

Table V: Time to cure

Recovery Time	Percentage
D9	37.6%
D14	18.5%
D21	27.1%
D28	10.5%
After D28	5.9%

DISCUSSION

This is a non-randomized observational study on the value of the HCQ/AZT combination in a population of patients with Covid 19 hospitalized in the ERAZZI University Hospital.

Three elements emerge from this observational study. The first is the low percentage of cardiovascular events with only one patient experiencing QT prolongation, which resulted in discontinuation of treatment. The second is the low number of deaths (note that all reported deaths had at least one comorbidity). The third is the high percentage of recoveries (85.32%), in a relatively short time (at D 14 more than half of the patients are already cured).

There is currently no specific treatment for COVID-19 and no vaccine. Current recommendations in France specify that HCQ is reserved for severe hospitalized cases. A recent retrospective study showed that HCQ administration was associated with a significant reduction in mortality in severe forms of COVID-19 [11]. In another non-randomized study where the authors used HCQ in severe forms of COVID-19, the results did not show an improvement in vital prognosis [12]. An observational study in New York City and District hospitals showed no difference in prognosis between the two groups - HCQ or not - in terms of in-hospital mortality or frequency of hospitalization [13]. The authors of a recent multinational observational study [14] showed a significant excess risk of ventricular arrhythmias in the group of patients treated with HCQ alone, risk multiplied by 2.4, and in the group of patients treated with HCQ combined with a macrolide (azithromycin or clarithromycin), risk multiplied by 5.1.

CONCLUSION

This non-randomized study, which has the limitation of being observational, shows that the combination of hydroxychloroquine or

chloroquine/azithromycin in patients with COVID-19, was associated with a real benefit in the majority of patients.

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