

Research Article

Evaluation of the Efficacy of the Combination of Hydroxychloroquine and Azithromycin in the Treatment of Covid-19 in a Moroccan Population

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Received: May 05, 2021; Accepted: June 12, 2021;

Published: June 19, 2021

Abstract

Context: Morocco has adopted the protocol combining hydroxychloroquine or chloroquine with azithromycin to treat patients with Covid-19, mainly based on Chinese studies and those of the IHU Mediterranee team in Marseille.

The objective of this study is to assess the effectiveness of this association in a Moroccan population.

Methods: We conducted a prospective descriptive analytical study at the center of virology, infectious and tropical diseases to assess the efficacy of hydroxychloroquine associated with azithromycin for the treatment of patients with Covid-19.

All patients hospitalized at the center between March 16, 2020 and May 16, 2020 were included in this study with a positive RT-PCR result for SARS-Cov2.

Results: 125 patients were hospitalized during this period meeting the inclusion criteria. All patients benefited from the combination of hydroxychloroquine and azithromycin. We studied the clinical, biological and CT parameters that could be associated with early viral clearance with a negative RT-PCR on D6 and D8.

The average age at diagnosis is 37.98 +/- 12.13 years. 121 patients (96.8%) are cured after 10 days of treatment. 32 patients (25.6%) had a viral clearance on D6 and D8. We did not find any factors significantly associated with early viral clearance.

Conclusion: Our study is inconsistent with work published by other teams regarding early viral clearance in patients treated with the combination of hydroxychloroquine and azithromycin, although clinical healing has been achieved in the majority of patients.

Keywords: COVID-19; Hydroxychloroquine; Azithromycin; Moroccan population

Introduction

Hydroxychloroquine is known for its immunomodulatory action widely used in autoimmune diseases. The antiviral action of hydroxychloroquine has been reported *in vitro*. Azithromycin also has an antiviral and anti-inflammatory action.

Chinese and Marseilles studies have shown that a combination of hydroxychloroquine and azithromycin is associated with healing in patients with covid-19. These studies confirm that this healing takes place early when the two molecules are combined.

The objective of our study is to assess the effectiveness of this association in a Moroccan population and to define the factors associated with early viral clearance in this population.

Materials and Methods

Demographic data on age, sex and co-morbidities were collected as well as the time between hospitalization and the onset of clinical

symptoms.

All patients hospitalized at the center between March 16, 2020 and May 16, 2020 were included in this study with a positive RT-PCR result for SARS-Cov2.

Patients were classified by severity according to the National Early Warning Score (NEWS) for COVID-19 [1]. Thoracic CT data as well as biological data (CRP, LDH, ferritinemia, lymphocyte count) were collected.

All the patients benefited from the therapeutic protocol combining hydroxychloroquine 600 mg per day in three doses for 10 days and azithromycin 500 mg on the first day then 250 mg from the 2nd to the 7th day. All patients were put on low molecular weight heparin at 0.6 ml per day with the addition of vitamin C at a dose of 3 g per day and vitamin D 100,000 IU in a single course. Ceftriaxone was also administered to patients with moderate to severe form.

The search for SARS-Cov-2 by RT-PCR after nasopharyngeal

swab was performed on admission and then on D6 of treatment. The patients with negative PCR on D6, were resumed 48 hours later.

Demographics, co-morbidities, time to diagnosis, severity of clinical presentation, biology and CT data were compared in patients with negative PCR on D6 and D8 and those with PCR that remained positive beyond from D6.

An electrocardiogram was performed on admission before treatment and then 48 hours from the start of treatment and then at the end of the 10 days of treatment. We did not notice any changes to the QT space.

Statistical analysis

Data analysis was carried out using SPSS software, version 13.0. The groups were compared using the khi2 test, and the univariate analysis by binary logistic regression.

Results

125 cases of covid-19 were hospitalized between March 16, 2020 and May 16, 2020 and met the inclusion criteria. All patients completed their 10-day treatment period. In 4 patients with no clinical improvement, treatment was extended by an additional 5 days or combined with an antiviral (Lopinavir/ritonavir). The different demographic, comorbidity, clinical, morphological and biological parameters were studied. The average age was 37.98 ± 12.13 years, 110 were men (88%) and 15 were women (12%). Regarding co-morbidities, 5 were hypertensive (4%), 3 were asthmatic (2.4%), 2 were diabetic (1.6%), and 2 had heart disease (1.6%). The average time for the average diagnosis is 5.83 days. 56 patients (44.8%) were asymptomatic. Morphologically, the CT scan was normal in 59 patients (47.2%), it showed minimal lesions (less than 10%) in 31 patients (24.8%), moderate lesions (between 10 and 25%) in 26 patients (20.8%), extensive involvement (between 25 and 50%) in 5 patients (4%) and severe involvement (more than 50%) in 3 patients (2.4%).

By adopting The national early warning score (NEWS) for COVID-19 [1], 73 patients (58.4%) had an asymptomatic or mild form of the disease, 48 patients (38.4%) a moderate form and 4 patients (3.2%) a severe form.

The study of the biological parameters shows a high CRP in 19.2%, a high LDH level in 29 cases (23.2%), a high ferritinemia in 19 cases (15.2%) and lymphopenia in 43 cases (34.4%).

The clinical cure retained on the disappearance of clinical symptoms and apyrexia more than 3 days was obtained in 121, or (96.8%) of the study population. 7 patients required oxygen therapy. One patient went to the intensive care unit for 48 hours and no deaths were reported.

After 6 days of treatment, 32 patients negated the PCR on D6 and D8, i.e. 25.6%. The patients who negated their PCR on D6 and D8 had rather a mild form of the disease, a normal chest CT scan or with minimal lesions, had a normal ferritin and a normal lymphocyte count (Table 2). However, the difference was not significant between the two groups. In the univariate analysis, no factor studied was significantly associated with early viral clearance (Table 3).

In our series, we did not observe any side effects in patients

Table 1: Population characteristics.

Characteristics	Values N=125
Age in years	37.98 +/- 12.13
Age < 40 years°	
No	58 (46.4)
Yes	67 (53.6)
Sex°	
M	110(88)
F	15(12)
The national early warning score (NEWS)	
Asymptomatic	55(44)
Mild	18(14.4)
Moderate	48(38.4)
Severe	4(3.2)
Critical	0
Comorbidities°	
No	109 (87.2)
Yes	16 (12.8)
Diagnosis delay <5 days°	
Non	40(32)
Oui	85 (68)
Pulmonary impact in CT scan°	
None	60 (48)
Minimal	33 (26.4)
Moderate	23 (18.4)
Extended	6 (4.8)
Severe	3 (2.4)
Critical	0
Normal CRP°	
No	24 (19.2)
Yes	101 (80.8)
Normal LDH°	
No	29 (23.2)
Yes	96 (76.8)
Normal Ferritinemia	
No	19 (15.2)
Yes	106 (84.8)
Low Lymphocytes count°	
No	82 (65.6)
Yes	43 (34.4)
Negative PCR in day 6 or 8	
No	93 (74.4)
Yes	32 (25.6)

treated with this combination and particularly no change in the QT space on the EKG.

Discussion

Our monocentric work using the combination of hydroxychloroquine and azithromycin shows viral clearance at one week of treatment in only 25.6% of patients.

In vitro studies have shown antiviral efficacy of Chloroquine (CQ) and Hydroxychloroquine (HCQ) against SARS-CoV2. This action is explained by, the alkalinization of the endosomes preventing the transport and the release of virions, an interference with the Angiotensin Converting Enzyme 2 (ACE2) preventing the penetration of the SARS-CoV2 virus in the cells and in addition an immunomodulatory and antithrombotic effect [2].

Synergistic effects of azithromycin and hydroxychloroquine against SARS-CoV2 have been observed *in vitro*, which appears to be reflected in clinical practice. Azithromycin is also a weak base and also accumulates in endosomes, with an alkalinizing effect equivalent to hydroxychloroquine. In addition to its antimicrobial properties, azithromycin is used for its immunomodulatory properties [2,3].

The use of this association has been based on Chinese and French

Table 2: Comparison of the negative day 6-8 PCR group and that of positive day 6-8 PCR.

	Négative PCR on day 6-8		p
	Yes (n=32)	No (93)	
Age <40 years° Yes	17 (53.1)	50 (53.8)	0.95
Sex° M	27 (84.4)	83 (89.2)	0.53
Asymptomatic or mild form (News score) Yes	22 (68.8)	51 (54.8)	0.16
Comorbidities yes	2 (6.3)	14 (15.1)	0.35
Diagnosis delay <5 days° yes	22 (68.8)	63 (67.7)	0.91
Normal lung or minimal impact° Yes	27 (84.4)	66 (71)	0.13
Normal CRP° Yes	25 (78.1)	76 (81.7)	0.65
Normal LDH° Yes	23 (71.9)	72 (77.4)	0.52
Normal ferritinemia° Yes	30 (93.8)	76 (81.7)	0.15
Low lymphocytes count° Yes	8 (25)	35 (37.6)	0.19

°Expressed in numbers and percentage.

Table 3: Factors associated with early virologic clearance in univariate analysis.

	Univariate analysis		
	OR	IC 95%	P
Age < 40 years° No	1	0.45-2.29	0.95
Yes	1.02		
Sex° M	1	0.20-2.07	0.46
F	0.65		
Asymptomatic or mild form (News score) No	1	0.23-1.29	.17
Yes	0.55		
Comorbidities No	1	0.57-12.4	0.21
Yes	2.65		
Diagnosis delay <5 days° No	1	0.40-2.26	0.91
Yes	0.95		
Normal lung or minimal impact° No	1	0.77-6.33	0.14
Yes	2.2		
Normal CRP° No	1	0.46-3.36	0.65
Yes	1.25		
Normal LDH° No	1	0.53-3.33	0.52
Yes	1.34		
Normal ferritinemia° No	1	0.065-1.36	0.12
Yes	0.29		
Low lymphocytes count° No	1	0.73-4.46	0.19
Yes	1.81		

studies. Jingzhou Guangzhou et al. [4] tested the efficacy and safety of chloroquine or hydroxychloroquine in the treatment of pneumonia associated with COVID-19 in 10 hospitals in Wuhan. This study, which included more than 100 patients, showed that chloroquine phosphate is superior to control to avoid worsening of pneumonia or to improve the results of pulmonary imaging and to favor a negatization of the viral load. No serious side effects were noted in this study.

Raoult et al. in a first uncontrolled study including 36 patients shows that hydroxychloroquine is significantly associated with a

reduction, or even a disappearance of the viral load in COVID-19 patients and its effect is reinforced by azithromycin [5]. The second study, also uncontrolled by the same center, on a series of 80 patients treated with the combination of hydroxychloroquine and azithromycin shows a negatization of the viral load in 83% of patients on D6 and 93% on D8 [6]. Another study by the same team from the Marseille Institute of Infectious Diseases, including 1,061 patients, showed a cure rate of 91.7% by using this combination. In this study, 10 patients (4.3%) went to intensive care with 5 deaths (0.47%), all aged 74 to 94 years [7]. Respiratory samples were cultured by La Scola et al. Samples with CT values of 13–17 were positive in culture. The positivity of the culture then gradually decreased as a function of the CT values, reaching 12% at 33 CT. After 5 days of treatment, 97.5% of the samples were negative. At the end of the 9th day, all the samples were negative [8].

A French observational study in 181 patients shows that the use of hydroxychloroquine is not associated with clinical benefit in patients with Covid-19 pneumonia [9]. A multinational, observational study influencing 96,032 Covid-19 patients shows that the use of hydroxychloroquine or chloroquine with or without macrolide was not associated with clinical benefit, but rather with an increased risk of cardiovascular events and death [10]. Factors associated with cardiovascular complications and death were, age, obesity, male, diabetes, high blood pressure, coronary artery disease, heart failure and arrhythmia.

Our series, although not homogeneous, including in particular many asymptomatic patients, suggests clinical cure with disappearance of clinical symptoms in the majority of patients, guaranteeing by referring to the work of the Mediterranean IHU, the absence of infectivity of the patients. However, our work does not agree with the data from the Marseille team regarding early viral clearance. However, it is important to note that in our study we did not find any side effects to the treatment.

References

- Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichun province, China. *Intensive Care Med.* 2020; 46: 357- 360.
- Felsenstein S, Herbert JA, McNamara PS, Hedrich CH. COVID-19: Immunology and Treatment Options. *Clin Immunol.* 2020; 215: 108448.
- Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-Cov-2 infection *in vitro*. *Cell Discov.* 2020; 6: 16.
- Gao J, Tian Z, Yang X. Chloroquine Phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends.* 2020; 14: 72-73.
- Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non randomized clinical trial. *International Journal of Antimicrobial Agents.* 2020.
- Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. *Travel Med Infect Dis.* 2020; 34: 101663.
- Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents.* 2020; 55: 105932.
- La Scola B, Le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, et al. Viral RNA load as determined by cell culture as a management tool for

- discharge of SARS-CoV-2 patients from infectious disease wards. *Eur J Clin Microbiol Infect Dis.* 2020; 39: 1059-1061.
9. Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. *medRxiv.* 2020.
 10. Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *The Lancet.* 2020.