Journal of Infectious Diseases & Therapy
ISSN: 2332-0877

Ennibiet K,et al., J Infect Dis Ther 2020, S2:003
DOI: 10.4172/2332-0877.1000003

Special Issue Article Open Access

Management of Covid-19 in Morocco: What Protocol and What Are the Factors Associated With Early Viral Clearance?

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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 June 16, 2020 was included in this study with a positive RT-PCR result for SARS-CoV-2.

Results: 186 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 36.29 ± 11.56 years. 182 patients (97.84%) were cured after 10 days of treatment. 51 patients (27.41%) had a viral clearance on D6 and D8. In the univariate analysis, the absence of lymphopenia was significantly associated with early viral clearance (p=0.036). In the multivariate analysis, young age less than 40 years and a normal Lactate Dehydrogenase level were associated with early viral clearance (p=0.014 and p=0.016).

Conclusion: Our study did not show 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

Study population

All patients COVID-19 hospitalized at the Center of virology, infectious and tropical diseases between March 16, 2020 and June 16, 2020 were included in this study.

Inclusion criteria were patients with a positive Real-Time Polymerase Chain Reaction (RT-PCR) result for SARS-CoV-2 at the admission.

Exclusion criteria were patients with a clinical or biological or morphological investigation that evocated COVID-19 and a RT-PCR negative at the admission.

Methods

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

Patients were classified by severity based on the National Early Warning Score (NEWS) for COVID-19 [1]. Thoracic CT data as well as biological data including C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), ferritinemia, lymphocyte count were collected for each patient.

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.

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Received: July 17, 2020; **Accepted date:** July 31, 2020; **Published date:** August 07, 2020

Citation: Ennibi K, Kasmy Z, Reggad A, Laatiris A, Aadi Y, et al. (2020) Management of Covid-19 in Morocco: What Protocol and What Are the Factors Associated With Early Viral Clearance? J Infect Dis Ther S2:003.

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

An electrocardiogram was performed on admission before treatment, 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

186 cases of COVID-19 were hospitalized between March 16, 2020 and June 16, 2020 and met the inclusion criteria. All patients completed their 10-days 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 socio-demographic data were as follow: the average age was 36.29 ± 11.56 years, 169 were men (90.9%) and 17 were women (9.1%). Regarding co-morbidities, 7 patients were hypertensive (3.76%), 5 were asthmatic (2.68%), 2 were diabetic type II (1.07%) and 3 had heart disease, coronary artery disease or heart failure (1.61%). The average time for the positive diagnosis of COVID-19 was 5.05 days. 84 patients (45.16%) were asymptomatic. Morphologically, the CT scan was normal in 99 patients (53.22%), it showed minimal lesions (less than 10%) in 44 patients (23.65%), moderate lesions (between 10% and 25%) in 29 patients (15.6%), extensive involvement (between 25% and 50%) in 11 patients (5.91%) and severe involvement (more than 50%) in 3 patients (1.61%).

According to the National Early Warning Score (NEWS) for COVID-19 (Table 1), 84 patients (45.16%) had an asymptomatic form of the disease, 35 patients (18.81%) a mild form, 62 patients (33.33%) a moderate form and 5 patients (2.69%) a severe form.

Characteristics	**Value N=186**
Age in years	36.29 ± 11.56
Age<40 years°	
No	70(37.6)
Yes	116(62.4)
Sex°	
M	169(90.9)
F	17(9.1)
Severity score NEWS°	
Asymptomatic	84(45.2)
Mild form	35(18.8)
Moderate form	62(33.3)
Severe form	5 (2.7)
Critical form	0
Co-morbidities°	
No	166 (89.2)
Yes	20 (10.8)
Time to diagnosis<5 days°	
No	47(25.3)
Yes	139(74.7)
Lung involvement on CT scan°	
Normal	99(53.2)
Minimal	44(23.7)
Moderate	29(15.6)
Extensive	11 (5.6)
Severe	3(1.6)
Critical	0
Normal CRP level°	
No	34(18.3)
Yes	152(81.7)
Normal LDH level°	
No	46(24.7)
Yes	140(75.3)
Normal Ferritinemia°	
No	25(13.4)
Yes	161(86.6)
Lymphopenia°	
No	124(66.7)
Yes	62(33.3)
Negative PCR on D6 D8°	
No	135(72.6)
Yes	51(27.4)
Note: °expressed as number and percentage	

Table 1: Population characteristics.

The study of the biological parameters showed a high CRP in 34 patients (18.28%), a high LDH level in 46 patients (24.73%), a high ferritinemia in 25 patients (13.44%) and lymphopenia in 62 patients (33.33%).

The clinical cure, retained on the disappearance of clinical symptoms and apyrexia for more than 3 days, was obtained in 182 representing 97.84% 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, 51 patients (27.41%) negated the PCR on D6 and D8. The patients who negated their PCR on D6 and D8 had rather a normal chest CT scan or with minimal lesions, had a normal ferritin and a normal lymphocyte count (Table 2). In the univariate analysis, the absence of lymphopenia was significantly associated with early viral clearance (p=0.036) (Table 3). In the multivariate analysis, young age less than 40 years and a normal LDH level at admission were associated with early viral clearance (p=0.014 and p=0.016) (Table 4).

	Negative PCR D6-D8		
	Yes (n=51)	**No (n=135)**	
Age<40 years°			
Yes	28(54.9)	88(65.2)	0.19
Sex°			
M	45(88.2)	124(91.9)	0.44
Asymptomatic or Mild form (NEWS)°			
Yes			
	36(70.6)	83(61.5)	0.24
Co-morbidities			
Yes	4(7.8)	16(11.9)	0.43
Time to diagnosis<5 days°			
Yes	38(74.5)	101(74.8)	0.96
Normal CT Scan or minimal lesions°			
Yes			
	44(86.3)	99(73.3)	0.062
Normal CRP level°			
Yes	41(80.4)	111(82.2)	0.77

Normal LDH level°			
Yes	35(68.6)	105(77.8)	0.19
Normal Ferritinemia°			
Yes	48(94.1)	113(83.7)	0.063
Lymphopenia°			
Yes	11(21.6)	51(37.8)	0.036
°expressed as number and percentage.			

Table 2: Comparison between negative PCR on D6-D8 group and positive PCR on D6-D8 group.

	Univariate analysis		
	0R	**IC 95%**	**P**
Age<40 years			
No	1		
Yes	1.53	0.79-2.62	0.19
Sex			
M	1		
F	0.66	0.23-1.9	0.44
Asymptomatic			
No	1		
Yes	0.65	0.34-1.24	0.19
Asymptomatic or Mild form (NEWS)			
No	1		
Yes	1.5	0.75-3.01	0.25
Co-morbidities			
No	1		
Yes	1.58	0.5-4.97	0.43
Time to diagnosis<5 days			
No	1		
Yes	1.01	0.48-2.13	0.96
Normal CT Scan or minimal lesions			
No	1		
Yes	2.28	0.94-5.53	0.07
Normal CRP level			
No	1		
Yes	1.12	0.49-2.56	0.77
Normal LDH level			
No	1		
Yes	1.6	0.78-3.27	0.19
Normal Ferritinemia			
No	1		
Yes	0.32	0.092-1.123	0.08
Lymphopenia			
No	1		
Yes	2.2	1.04-4.68	0.04

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

	Multivariate analysis		
	0R	**IC 95%**	**P**
Age<40 years			
No	1		
Yes	2.58	1.20-5.52	0.014
Asymptomatic			
No	1		
Yes	0.9	0.44-1.86	0.79
Normal CT Scan or minimal lesions			
No	1		
Yes	2.05	0.65-6.43	0.21
Normal LDH level			
No	1		
Yes	2.76	1.20-6.33	0.016
Normal Ferritinemia			
No	1		
Yes	0.31	0.06-1.52	0.15
Lymphopenia			
No	1		
Yes	2.15	0.93-4.94	0.71

Table 4: Factors associated with early virologic clearance in multivariate analysis.

In our series, we did not observe any side effects in patients treated with this combination and particularly no change in the QT space on the electrocardiogram.

Discussion

Our monocentric work using the combination of hydroxychloroquine and azithromycin in treatment of COVID-19 patients showed viral clearance at one week of treatment in only 27.41% of patients.

In vitro studies have shown antiviral efficacy of Chloroquine (CQ) and Hydroxychloroquine (HCQ) against SARS-CoV-2. 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-CoV-2 virus in the cells and in addition an immunomodulatory and antithrombotic effect [2].

Synergistic effects of azithromycin and hydroxychloroquine against SARS-CoV-2 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 alkalizing effect equivalent to hydroxychloroquine. In addition to its antimicrobial properties, azithromycin is used for its immunomodulatory properties [2,3].

The use of this association, for the emergent COVID-19 treatment, has been based on Chinese and French studies. Jingzhou 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, to improve the results of pulmonary imaging and to favour a negativation 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 showed a negativation 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].

However, some studies reported that hydroxychloroquine has no clinical benefit in treating patients with COVID-19. Indeed, a French observational study in 181 patients showed that the use of hydroxychloroquine is not associated with clinical improvement in patients with COVID-19 pneumonia [9]. Although, neither the benefit, nor the impairment could be determined for the chloroquine so far, because of absence of controlled and randomized studies, a special care should be observed regarding formal contraindicating of using this product.

Our case, although not homogeneous, including in particular many asymptomatic patients, suggests clinical cure with disappearance of clinical symptoms in the majority of patients (97.84%) at day 10 of treatment, 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.

Although, it is important to note that in our study we did not find any side effects to the treatment. This might be explained by many positive prognosis factors in our patients which are relatively young age and the absence of severe co-morbidities.

Conclusion and Perspective

Our study did not show early viral clearance in patients treated with the combination of hydroxychloroquine and azithromycin, although clinical healing has been achieved in the majority of patients (97.84%), among them 84 were asymptomatic (45.16%) and 164 with no co-morbidities (88.17%) . It is also to be pointed out that clinicians should be aware regarding the using of chloroquine in patients with severe co-morbidities.

However, controlled studies are needed to assess the real efficacy of hydroxychloroquine combined azithromycin in the treatment of COVID-19 patients.

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