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Azithromycin and Hydroxychloroquine Accelerate Recovery of Outpatients with Mild/Moderate COVID-19

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Authors' contributions

This work was carried out in collaboration among all authors. Authors VG and JLT designed the study and wrote the first draft of the manuscript. Authors VG, TL, ES, NRA, P. Lacrosse and MW followed the patients. Author P. Lévy performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The challenge regarding COVID-19 is to prevent complications and fatal evolution. Azithromycin (AZM) and hydroxychloroquine (HCQ) have proven their antiviral effect *in vitro*. We aimed to assess the efficacy and safety of AZM alone or combined to HCQ, prescribed, at an early stage, in patients with Covid-19, in a primary care setting.
Study Design: Retrospective observational study.
Place and Duration of Study: Patients have been followed by private practitioners in France, between March and April 2020.
Methodology: Eighty-eight patients received either no or a symptomatic treatment (NST) (n=34) or AZM alone (n=34) or AZM+HCQ (n=20). The efficacy end point was the time to clinical recovery

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and the safety end point was the occurrence of cardiovascular events. To improve the evidence level, a case-control analysis was performed on a sample of 57 patients (19/group) matched for age, sex and BMI.

Results: The mean (SD) times to achieve clinical recovery were respectively 25.8 days (11.1), 12.9 days (13.4) and 9.2 days (9.3), showing a statistically significant difference between NST and AZM alone ($p<0.0001$) or AZM+HCQ ($p<0.0001$). The statistical difference between NST and AZM was confirmed ($p=0.0149$) as well as the difference with AZM+HCQ ($p=0.0002$). No cardiac toxicity was recorded in any patient. No statistical difference was shown between AZM and AZM+HCQ groups, although the dual therapy tended to be more effective in patients over 50 years, based on an analysis using the cox model.

Conclusion: AZM and AZM+HCQ favourably impacted the course of the disease. We need trials, ideally prospective/double blind, to show if a statistical difference can be evidenced with a broader group, and clarify the indications of each treatment depending on initial clinical presentation.

Keywords: COVID-19; SARS-CoV-2; azithromycin; hydroxychloroquine; primary care.

1. INTRODUCTION

Corona virus infectious disease 2019 (COVID-19) has mainly a favourable outcome and asymptomatic SARS-CoV-2 carriage may be observed in some persons. However, patients can decompensate at any time and effective therapies are urgently needed in this pandemic period. The disease progresses in two phases; the first which we could describe as an influenza-like illness, the second dominated by a respiratory distress syndrome, cardiovascular symptoms and other immune anomalies. The challenge is to treat very early to prevent complications and fatal evolution.

Different molecules have been tested during this COVID-19 pandemic, in *vitro* and *in vivo* at different stages of the disease [1,2].

Several studies carried out *in vitro* indicate that chloroquine exerts direct antiviral effects on several viruses [3], including the coronaviruses [4], and in particular SARS-CoV-2, agent responsible for the COVID-19 pandemic [5,6,7]. It works by inhibiting the entry of the virus into cells by increasing the endosomal pH required for fusion of the virus with the cells, but also by inhibiting replication by interfering with glycosylation of cellular receptors for the virus.
These are data obtained from cell cultures, but the inhibitory concentrations are of the same order as those obtained in the plasma of patients treated for malaria or rheumatoid arthritis [7,8].

Hydroxychloroquine (HCQ) also has antiviral effects demonstrated *in vitro* on human cells cultured and infected with several viruses, including coronaviruses [9]. These effects have been confirmed recently for SARS-CoV-2, on primate cells, the inhibitory concentrations being of the same order as those observed in therapy [10,11].

HCQ has a better safety profile than chloroquine and hence makes it a more preferable drug.

The choice of azithromycin (AZM) to be associated with HCQ, is not only due to the very wide use of this antibiotic in pulmonary infections, but also because it also has antiviral activity *in vitro*. It has been demonstrated on cultured human bronchial cells from patients with chronic bronchitis; in this model, AZM reduces the viral load and increases the secretion of interferon (a factor released by infected cells to inhibit the proliferation of the virus in neighboring cells) [12].

Gautret et al. [13], which have shown that the HCQ / AZM association rapidly dissipates the viral load of patients infected with COVID-19, also demonstrated a synergistic action of these two drugs to inhibit the proliferation of the virus in infected cells, at concentrations identical to those observed in treated patients.

In addition to its antiviral activity, HCQ, have an immunomodulatory and anti-inflammatory activity, used in the treatment of autoimmune diseases. The mode of action is complex, different from that of glucocorticoids and immunosuppressants [14].

In this study we aimed to assess the efficacy and safety of azithromycin alone or combined to hydroxychloroquine, prescribed, at an early stage, in COVID-19 patients.

The rational for this evaluation was the results published by Gautret et al. [13] which evidenced a possible efficacy of these molecules when prescribed at an early stage of the disease.

The study has been performed by a group of French medical doctors, who initially intended to conduct a prospective study in medical doctors tested COVID+ by PCR test, and volunteers for an auto-treatment by the combination of AZM and HCQ.

Following the ban on hydroxychloroquine by the French Health Authorities (26th march 2020), for MDs working in private practice, the group decided to conduct a retrospective study.

2. METHODOLOGY

2.1 Data Source and Study Design

The 88 patients included in this study were patients followed by the MDs, who were volunteers to follow and treat 1.000 colleagues COVID+ in the initially planned prospective study. The patients were MDs themselves or members of their families and caregivers.

They were asked to centralize in a data-base, the data of colleagues, their families and caregivers that they followed for COVID-19. The patients had to give their consent for the use of their anonymized data for publication.

The study is a retrospective study analysing three types of treatments and the main evaluation criteria is the time to clinical recovery (time between symptom onset and last day of symptom). Adverse events were collected, their evolution was evaluated and accountability to drugs was evaluated. Data were centralized in a file declared to CNIL (Commission Nationale de l'Informatique et des Libertés).

2.2 Clinical Data Collection

Patients were all outpatients, older than 18-years old, suffering from influenza-like illness symptoms (fever, cough and sore throat); their data were recorded in the medical files that each doctor in private practice must archive. Information about symptoms, treatments received, and course of illness were collected. Comorbidities and background treatments were retrieved from medical files. Symptoms of COVID-19 were documented, in particular those listed as follows: fever, sweating, chills, fatigue, headache, cough, nasal obstruction, sore throat, dyspnoea, anosmia, ageusia, diarrhoea, nausea, vomiting and dizziness. When possible, other relevant clinical data were collected, in addition to the results of chest computed tomography (CCT) and to those of SARS-CoV-2 PCR assay on nasopharyngeal swab, when carried-out. Since PCR tests were not available on a regular basis in private practice (lack of test availability in private laboratories), patients with symptoms of COVID-19 in close contact with a PCR confirmed case were considered COVID-19 probable cases (e.g.: spouse of a MD with a positive test).

The efficacy criterion was the time to complete clinical recovery.

2.3 Treatment

Patients were classified in three groups according the treatment they received: 1) no or symptomatic treatment (NST) (most often paracetamol on demand); 2) AZM only (500 mg on day 1 followed by 250 mg per day for the next four days) ; 3) AZM+HCQ (600 mg per day for seven to ten days).

The choice of treatments was based on contraindications in some patients and availability of drugs. HCQ was prescribed before the publication of the French decree restricting its use to hospitals. The treatments were given under the responsibility of prescribers after information of patients on the benefits and risks and obtaining their consent. All subjects treated with HCQ underwent an electrocardiogram before treatment and 48 hours after its start.

2.4 Statistical Analysis

The comparisons between groups were made using Kruskal-Wallis test and Mann-Whitney test for quantitative variables and using the Chi2 test or Fisher's exact test for categorical variables, with Bonferroni adjustment. A case-control sub-analysis was performed on a sample of 57 patients (19 per group) matched for age, sex and body mass index (BMI).

Moreover, the three patient groups rates were estimated with the Kaplan-Meier method and compared with Logrank test or Breslow-Gehan-Wilcoxon test. The censured variable was recovery versus death or hospitalization. Prognosis factors were subjected to univariate and multivariate analyses using a descending stepwise Cox model. Candidate variables were

selected with p≤0.2. This analysis was consolidated with boostrap method using two hundred iterations. A two-side p-value of 0.05 defined significance.

All statistical analyses were computed with Statview® 5.0, Biostatgv® and Stata® 11.2.

3. RESULTS AND DISCUSSION

3.1 Baseline Data of Patients

Eighty-eight outpatients with COVID-19 agreed to participate in the study. They all had symptoms suggestive of COVID-19, most often influenza-like illness symptoms, as described in Table 1.

A total of 51 patients (58%) were PCR-confirmed. The other 37 patients who did not benefit from PCR testing were probable cases. A SARS-CoV-2 positive serology was found in five patients not initially PCR tested, increasing *a posteriori* to 64% the biological proof of diagnosis (Table 2).

Twenty patients underwent a CCT. Lesions compatible with pneumonia (ground-glass opacities) were found in 15 patients, among them, four patients were not tested, leading to a 68.2% diagnosis on paraclinical data. A pericarditis was observed in one patient.

There were 34 subjects treated with AZM alone and 20 with AZM+HCQ. Due to lack of AZM, availability in pharmacies, clarithromycin was prescribed to two patients.

NST group included 11 patients without any treatment and 23 who received symptomatic treatment (paracetamol for 20 of them). The treatments started early after the onset of symptoms, the day of onset for 36 patients (41%) and within 15 days for the others, except for one patient which started treatment at day 40 in the AZM group.

The baseline demographic and clinical characteristics of patients in the three treatment groups are shown in Table 1. Of the 88 patients [mean age of 48.8 years, 46 (52.3%) were men, 12 (13.6%) were obese, 11 (12.8%) had hypertension and three (3.4%) diabetes. None of the patients had cancer, kidney failure or immunodeficiency. Demographic data and comorbid conditions were not statistically different between the three treatment groups.

Fatigue, headache, cough and fever were the most common symptoms, present at the time of diagnosis in at least two-third of patients. The prevalence of symptoms was not statistically different between the three groups, except for fever (p=0.023), chills (p=0.021), dyspnoea (p=0.012) and anosmia (p=0.038). Comparison of groups two to two showed that fever was significantly more frequent in the AZM+HCQ group than in the AZM alone group (84.2% vs 48.5%, p=0.011), with a significantly different body temperature at baseline between these two groups (median: 38.4 vs 37.6°C, p=0.010). The other statistically significant differences between each group and the NST group were as follows: higher prevalence of dyspnoea in the AZM+HCQ group (p=0.004), higher prevalence of chills (p=0.009) and lower prevalence of anosmia (p=0.011) in the AZM alone group.

The other symptoms reported by the patients were distributed in three system organ classes (SOC): thoracic disorders (mainly chest tightness), nervous system disorders and skin disorders.

3.2 Efficacy Outcomes

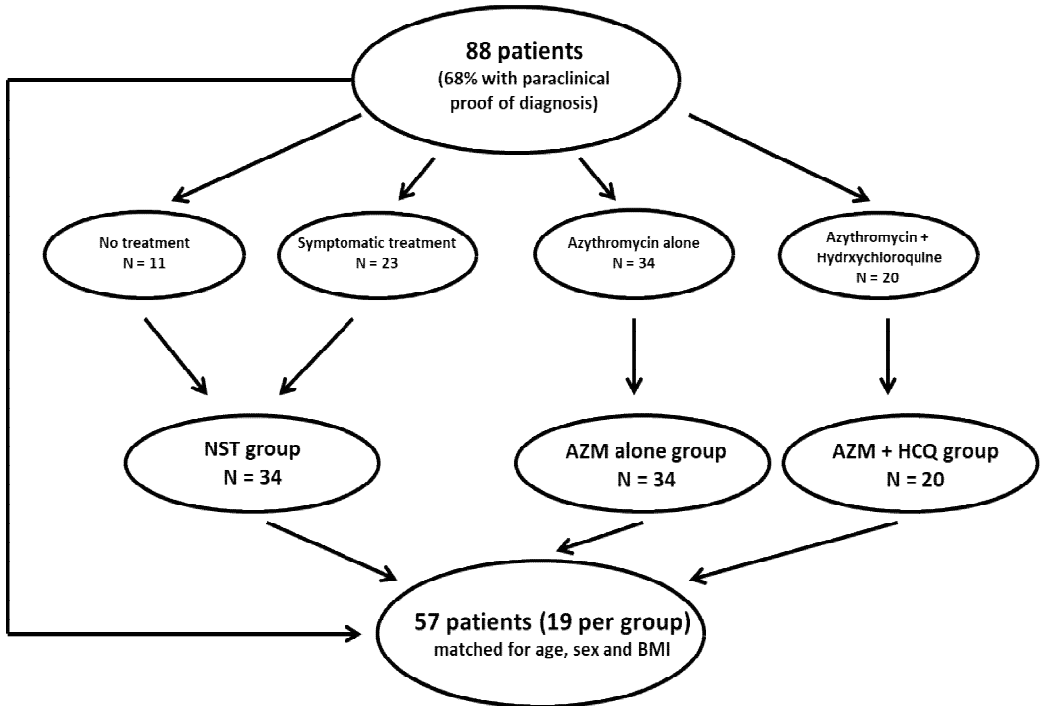
Overall, the clinical condition improved in 89.8% of patients (88.2% in the NST, 91.2% in the AZM alone group and 90.0% of the AZM+HCQ group).

As shown in Table 3 and in Fig. 1, the time to clinical recovery was significantly different between the three groups comparing as well the mean recovery time (p<0.0001), as the survival curves (p<0.0001). Compared to the NST group (mean time = 25.8 days), the recovery was significantly faster in the AZM alone group (mean time 12.9 days, p<0.0001, survival p<0.007) and in the AZM+HCQ group (mean time 9.2 days, p<0.0001, survival p<0.0001). There was no statistically significant difference between the AZM alone and the AZM+HCQ groups (mean time p=0.26, survival p<0.18). The case-control analysis performed on the sample of the 57 patients matched for age, sex and body mass index found similar values for the time to clinical recovery and survival with the same differences between groups.

The Cox model identified treatment, age and initial diastolic blood pressure as prognosis factors for time to clinical cure, but only treatment and age remained clearly stable at bootstrap with a threshold of 50 years [HR (95% CI): 2.37 (1.30 – 4.30), p= 0.0047]. More precisely, below 50 years of age, AZM alone and AZM+HCQ greatly

shortened the time to clinical cure, with a clear superiority of the dual therapy (Fig. 2A). Above this age, the dual therapy had the same effect, although less effectively than in patients below 50 years of age, while AZM had no effect on a proportion of patients, compare to the NST group (Fig. 2B, end of the survival curve).

In addition, as shown in Fig. 3, it is obvious that the AZM+HCQ treatment clearly preserved patients over 50 years.



Flow chart

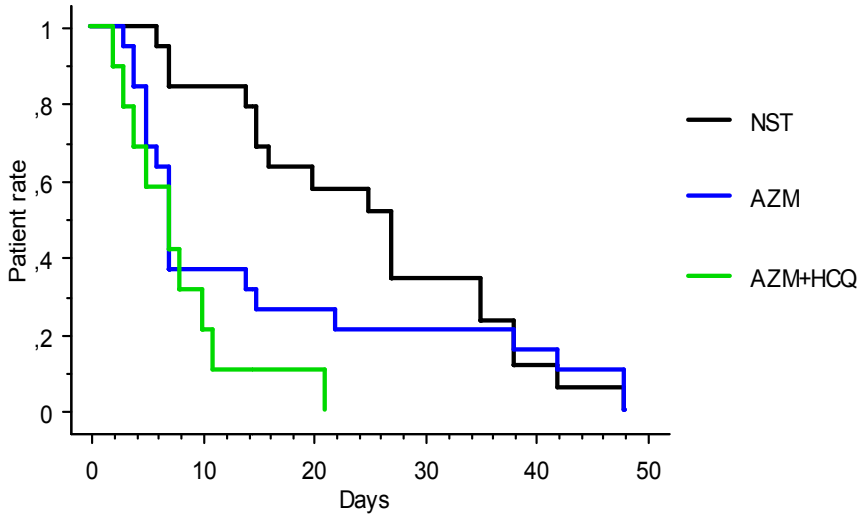


Fig. 1. Kaplan-Meier curve for time to complete clinical cure comparing treatment groups (case-control subanalysis)

Table 1. Baseline demographic and clinical characteristics of the patients

	Total (n=88)	NST (n=34)	AZM (n=34)	AZM+HCQ (n=20)	p value
Age – yr					
Median (range)	52 (18 – 93)	49 (19 – 81)	53 (18 – 93)	54 (32 – 72)	0.36
Male sex – no (%)	46 (52.3)	20 (58.8)	14 (41.2)	12 (60.0)	0.25
BMI – kg/m^2					
Median	24.4	24.5	24.7	24.2	0.97
Range	17.8 – 40.6	18.8 – 36.0	19.2 – 38.2	17.8 – 40.6	
Comorbidities-no (%)					
Any heart disease	15 (17.2)	6 (17.6)	4 (11.8)	5 (26.3)	0.38
Hypertension	11 (12.8)	4 (11.8)	3 (9.1)	4 (21.1)	0.46
Coronary disease	2 (2.3)	1 (2.9)	1 (3.0)	0	1
Heart dysrhythmia	1 (1.2)	1 (3.0)	0	0	1
Diabetes	3 (3.4)	1 (2.9)	1 (2.9)	1 (5.0)	0.45
Obesity	12 (13.6)	3 (3.4)	7 (20.6)	2 (10.0)	0.38
Symptoms – no (%)					
Fever	56 (65.1)	24 (70.6)	16 (48.5)	16 (84.2)[a]	0.023*
Sweating	42 (48.8)	16 (47.1)	15 (45.5)	11 (57.9)	0.66
Chills	51 (59.3)	14 (41.2)	24 (72.7)[b]	13 (68.4)	0.021*
Fatigue	70 (81.4)	24 (70.6)	28 (84.8)	18 (94.7)	0.08
Myalgia	54 (62.8)	24 (70.6)	18 (54.5)	12 (63.2)	0.40
Headache	59 (69.4)	22 (66.7)	24 (72.7)	13 (68.4)	0.86
Cough	57 (65.5)	22 (66.7)	22 (66.7)	13 (65.0)	0.98
Nasal obstruction	27 (31.8)	12 (35.3)	10 (32.3)	5 (25.0)	0.73
Sore throat	27 (31.8)	8 (23.5)	15 (46.9)	4 (21.1)	0.07
Dyspnoea	35 (41.7)	8 (23.5)	15 (48.4)	12 (63.2)[b]	0.012*
Anosmia	35 (40.7)	19 (55.9)	8 (25.0)[b]	8 (40.0)	0.038*
Ageusia	29 (33.7)	16 (47.1)	8 (25.0)	5 (25.0)	0.11
Nausea	21 (25.6)	5 (15.2)	9 (30.0)	7 (36.8)	0.18
Diarrhoea	29 (35.4)	11 (33.3)	10 (33.3)	8 (42.1)	0.78
Vomiting	2 (2.4)	1 (3.0)	0	1 (5.2)	0.49
Dizziness	12 (14.6)	8 (24.2)	2 (6.7)	2 (10.5)	0.12
Any other symptom	35 (39.8)	13 (38.2)	13 (38.2)	9 (45.0)	0.86
Body temperature–°C					
Median	38.0	38.0	37.6	38.4	0.021*
Range	36.0 – 41.0	36.0-39.7	36.2 – 41.0	36.7 – 41.0	
Respiratory – bpm					
Median	17.0	18.0	16.0	16.5	0.80
Range	12 – 50	12 – 50	16 – 25	14 – 30	

:comparison between the three treatment groups statistical (Kruskal-Wallis test or Chi 2 test, p<0.05)
[a]:p=0.011 (comparison with the AZM alone group by Mann-Whitney test with Bonferroni adjustment)
[b]:p<0.017 (comparison with the NST group by Mann-Whitney test with Bonferroni adjustment)

Table 2. PCR tests and CCT

	Total (n=88)	NST (n=34)	AZM (n=34)	AZM+HCQ (n=20)	p value
Positive PCR test (%)	51 (58)	20 (59)	17 (50)	14 (70)	0.35
Chest scan (%)	20 (23)	5 (15)	7 (21)	8 (40)	0.13
COVID lesions (%)	16 (18)	4 (12)	7 (21)	5 (25)	0.91

Under treatment, the clinical condition of seven patients (two in the NST group, three in the AZM alone group, two in the AZM+HCQ group) worsened, requiring hospitalization in four of them. One patient, a man of 82-year-old without comorbidities in the NST group died suddenly; the three others recovered and left the hospital at day 4 and day 6 (AZM+HCQ group), and at day 10

(NST group). One patient of each group received invasive ventilation. Respiratory disorders were the cause of aggravation in all cases, except for one man treated with AZM, who developed a quadranopsy.

3.3 Safety Outcomes

No serious adverse event neither cardiovascular events were reported in any treatment group. There were five patients (5.7%) who reported at least one non-serious adverse event: one in the NST group (diarrhoea) and four in the AZM+HCQ group, respectively: 1) gastrointestinal disorders, 2) urticaria and headache, 3) gastrointestinal disorders and headache, 4) nausea and headache. Only two adverse events were considered as related to treatment (gastrointestinal disorders in a patient treated with AZM+HCQ and in another treated with paracetamol).

Table 3. Time to clinical recovery (days)

		Total	NST (1)	AZM (2)	AZM+HCQ (3)
Analysis of all patients	No	88	34	34	20
	Median	10.5	27.0	7.0	7.0
	Range	2 – 48	6 – 48	3 – 48	2 – 40
	Mean (SD)	17.1 (13.6)	25.8 (11.1)	12.9 (13.4)	9.2 (9.3)
	p values	Comparison* of the 3 groups: p < 0.0001			
		Comparison** of groups 1 - 2: p < 0.0001			
		Comparison** of groups 1 - 3: p < 0.0001			
		Comparison** of groups 2 - 3: p = 0.26			
	Logrank	Comparison* of the 3 groups: p < 0.0001			
		Comparison** of groups 1 - 2: p = 0.007			
		Comparison** of groups 1 - 3: p < 0.0001			
		Comparison** of groups 2 - 3: p = 0.18			
Case-control analysis	No	57	19	19	19
	Median	10.0	27.0	7.0	7.0
	Range	2 – 48	6 – 48	3 – 48	2 – 40
	Mean (SD)	16.6 (14.2)	24.8 (12.5)	15.5 (15.9)	9.5 (9.4)
	p values	Comparison* of the 3 groups: p = 0.001			
		Comparison** of groups 1 - 2: p = 0.0149			
		Comparison** of groups 1 - 3: p = 0.0002			
		Comparison** of groups 2 - 3: p = 0.33			
	Logrank or Breslow-Gehan-Wilcoxon	Comparison* of the 3 groups: p = 0.001			
		Comparison** of groups 1 - 2: p = 0.011			
		Comparison** of groups 1 - 3: p < 0.001			
		Comparison** of groups 2 - 3: p = 0.15			

*: *Kruskal-Wallis test (significant if p<0.05)*

**: *Mann-Whitney or Logrank test with Bonferroni adjustment (significant if p<0.017)*

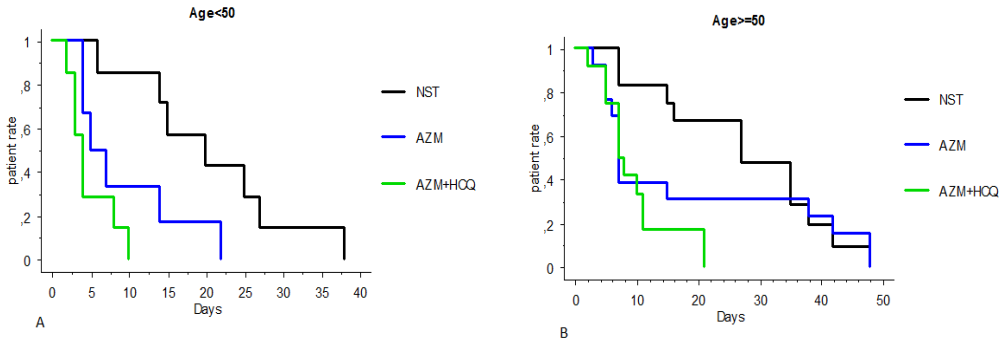


Fig. 2. Kaplan-Meier curve for time to complete clinical cure comparing treatment groups according to age (Paired data)

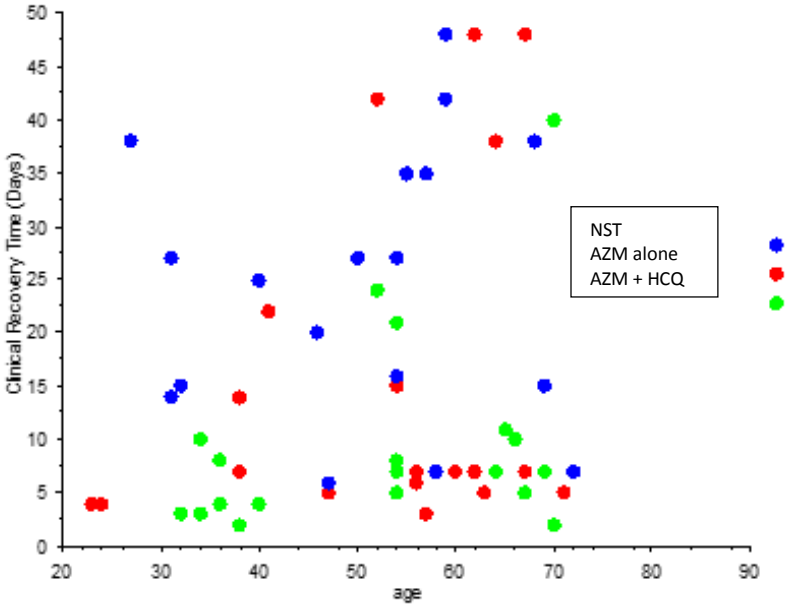


Fig. 3. Distribution of time to clinical cure according to age in patients matched for age, sex and BMI (19 per group)

3.4 Discussion

This report describes the clinical outcome in a mild/moderate COVID-19 infection and shows that the early treatment with AZM given alone or in combination with HCQ is associated with a statistically significant shorter time to clinical recovery. Although this result comes from an observational retrospective study including a small number of patients, it is confirmed by a case-control analysis controlling age, gender and BMI.

All patients included were symptomatic, diagnosis of COVID-19 was made clinically and was confirmed in 68.2% of the patients on paraclinical data.

As in the Barbosa et al. study [15] conducted in Brazil by general practitioners, we had to face the difficulties of a study performed in outpatients during a pandemic period with non-availability of personal protections, tests and even medications.

Overall, 90% of the patients improved, which is consistent with what is known about the evolution of the disease [16]. In this study, patients were treated at the early stage of the disease, with 40% of them starting treatment at day 1 of the course of the disease. Such surveys conducted in a primary care context are of paramount importance given that patients seen at an early stage of the disease should be targeted to benefit from treatment before complications occur. We also advise clinicians to screen not only dyspnoea at rest, but also exertional dyspnoea which might be more sensitive to detect pulmonary lesions.

AZM and AZM+HCQ clearly favourably impacted the resolution time of the symptoms. Our results are consistent with the one published by Chen et al. [17] who concluded from a randomized clinical trial including 62 patients that the time to clinical recovery was shortened by HCQ alone. These results are in agreement with those of Million et al. in an open study which included more than 1.000 subjects [18], those of Arshad et al. [19] and those of Lagier et al. [20] which reports the outcomes of 3.737 patients treated with HCQ alone, HCQ+AZM or AZM alone.

Shortening the evolution time is not only clinically important, but has also social consequences, for example by reducing the length of work stoppages. Furthermore, four patients needed to be hospitalized for worsening. Three of them (two in the AZM+HCQ group and one in the NST group) recovered, the fourth (NST group) died. Barbosa et al. study [15], conducted in 636 symptomatic outpatients, followed by telemedicine showed that AZM+HCQ association allowed a

drastic reduction in the number of hospitalizations compared to the control group ($p<0.001$) [15].

In our study we did not find a significant difference between the treatment by AZM alone and AZM+HCQ with regard to time recovery. Nevertheless, the Cox model showed that age was a predictor of time to clinical cure and that the AZM + HCQ combination tended to be more effective than AZM alone, especially in patients over 50 years.

Randomized double-blind clinical trials are needed to better investigate potential differences in efficacy end-points between AZM and AZM+HCQ treatment. Due to the non-availability of HCQ for outpatients, the AZM+HCQ group was smaller in our study.

We also have to clarify the indications of each treatment depending on initial symptoms.

When given at an early phase of the disease, AZM and HCQ have an antiviral effect, and their synergy and tolerability have been shown in four studies [13,18,21,22] with a higher reduction of viral load when they are combined. Virus cultures from patient's respiratory samples were negative in 97.5% patients at day 5 of treatment [21].

The interest of combining these two molecules is also to achieve an antiviral effect using doses currently prescribed in general practice.

In the first study published by Gautret et al. [13] mean plasmatic level of HCQ was 0.46 µg/ml (1.37 µM) in 20 patients treated with 600 mg HCQ/day during 10 days. Garcia-Cremades et al. [23] integrating pharmacological, clinical and virological data obtained in 116 patients infected with SARS-CoV-2 and treated with HCQ, concluded that plasmatic levels of the molecule were comparable to effective *in vitro* concentrations and that therapeutic dose might be between 400 and 600 mg/day. Finally, the pertinence of a 600 mg/day dose has been confirmed by a Chinese study using a pharmacological model from *in vitro* data [10].

It is highly probable that an early negativation of the viral load impacts the course of the disease.

Considering the second phase of the disease, AZM is likely acting in preventing secondary development of bacterial pneumonia and we have to clarify how immunomodulative properties of HCQ might be of interest in preventing and/or treating some inadequate immune responses leading to vascularitis-like disorders.

It will also be essential to check if the sequelae of the infection, in particular pulmonary fibrosis, will be different in the group treated with AZM than that treated with AZM+HCQ.

Finally, we have to stress that tolerance was globally good in all groups and that no cardiac toxicity was recorded, results which are consistent with the one published by Kim et al. [22] and also found in other studies when the patients were carefully monitored [19,20].

HCQ is a COVID-19 treatment prescribed for 7 to 10 days, which avoids adverse events observed in long-term treatments that can be observed during chronic treatments for rheumatological purposes.

Saleh et al. [24] evaluated the effect of chloroquine, HCQ and AZM on the corrected QT interval in hospitalized patients with SARS-CoV-2 infection. Seven patients (3.5%) out of 201 patients required discontinuation of these medications due to QTc prolongation; and there was no report of arrhythmogenic deaths. In conclusion, when we respect the contraindications of these drugs, they can be used safely.

4. CONCLUSION

This study confirms that AZM or AZM+HCQ combination given early are safe and effective treatments for COVID-19 and can be prescribed in a primary care setting. Furthermore, we must keep in mind that the viral shedding persistence being fundamental on the contagiousness parameter, the association AZM+HCQ is the best combination to negative viral load, so far.

As stressed before, we need further studies comparing AZM and AZM+HCQ treatment. Awaiting these studies, and in the absence of contraindication, we recommend the association AZM+HCQ in first intention. The chemoprophylaxis studies in progress with HCQ for COVID-19 must also be followed with interest in a more general reflection on public health.

CONSENT

Informed consent to receive the treatment has been given by all patients.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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