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Short Communication

A comprehensive strategy for the early treatment of COVID-19 with azithromycin/hydroxychloroquine and/or corticosteroids: Results of a retrospective observational study in the French overseas department of Réunion Island

Arthur Dubernet[a], Kevin Larsen[a], Laurie Masse[a], Jérôme Allyn[b,c], Emilie Foch[a], Lea Bruneau[d,e], Adrien Maillot[e], Marie Lagrange-Xelot[f], Vincent Thomas[g], Marie-Christine Jaffar-Bandjee[g], Loraine Gauzere[h], Loic Raffray[h], Karine Borsu[i], Servane Dibernardo[i], Stéphane Renaud[j], Michel André[a], Diane Moreau[a], Julien Jabot[b], Nathalie Coolen-Allou[a], Nicolas Allou[b,c,*]

[a] Pneumologie, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France
[b] Réanimation polyvalente, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France
[c] Département d'Informatique Clinique, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France
[d] INSERM CIC 1410 Clinical and Epidemiology, University Hospital, Saint Pierre, Réunion Island, France
[e] Department of Public Health and Research Support, Methodological Support and Biostatistics Unit, University Hospital, Saint Denis, Réunion Island, France
[f] Service des Maladies Infectieuses, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France
[g] Microbiologie, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France
[h] Médecine Interne, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France
[i] Médecine Polyvalente, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France
[j] Gériatrie, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France

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ABSTRACT

Background: This study aimed to evaluate the prognosis of COVID-19 patients in Reunion Island, with a particular focus on the management of patients with hypoxemic pneumonia.
Methods: This retrospective observational study was conducted from 11 March to 17 April 2020 at the only hospital authorized to manage patients with COVID-19 in Reunion Island.
Results: Over the study period, 164 out of 398 patients (41.2%) infected with COVID-19 were admitted to Félix Guyon University Hospital. Of these, 36 (22%) developed hypoxemic pneumonia. Patients with hypoxemic pneumonia were aged 66 [56–77] years, 69% were male and 33% had hypertension. Ten patients (27.8%) were hospitalized in intensive care unit (ICU). Hydroxychloroquine/azithromycin treatment was associated with a lower ICU admission rate ($P = 0.008$). None of the 6 patients treated with corticosteroids were hospitalized in ICU ($P = 0.16$). There were no deaths at follow up (minimum 80 days).
Conclusions: Despite the risk profile of COVID-19 patients with severe hypoxemic pneumonia, the mortality rate of the disease in Reunion Island was 0%. This may be due to the care bundle used in our hospital (early hospitalisation, treatment with hydroxychloroquine/azithromycin and/or corticosteroids, non-invasive respiratory support, etc).

1. Introduction

Réunion Island (845 000 inhabitants) is a French overseas department located in the Indian Ocean at a distance of 10 000 km from Paris. On 17 April 2020, a total of 398 cases of coronavirus disease 2019 (COVID-19) had been reported in Réunion Island (first case detected on 11 March 2020) [1]. More than 70% of these cases were imported from Europe, which was the epicentre of the

* Corresponding author at: Réanimation polyvalente, Centre Hospitalier Universitaire Felix-Guyon, Allée des Topazes, 97405 Saint Denis, Réunion Island, France.
E-mail address: nicolas.allou@hotmail.fr (N. Allou).

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pandemic at the time. The aim of this study was to evaluate the prognosis of COVID-19 patients in Réunion Island, with a particular focus on the medical management of patients with hypoxaemic pneumonia.

2. Methods

2.1. Study outline

This study was approved by the Ethics Committee of the French Infectious Diseases Society and was declared to the Commission nationale de l'informatique et des libertés. This retrospective observational study was conducted from 11 March 2020 to 17 April 2020 at the only hospital authorised to manage COVID-19 patients in Réunion Island. Patients were systematically hospitalised in the following cases: pneumonia; sepsis and co-morbidities (age >65 years, diabetes mellitus, heart disease, chronic respiratory disease, cancer, chronic kidney disease, etc.). All patients with hypoxaemic pneumonia (i.e. pneumonia requiring oxygen to achieve oxyhaemoglobin saturation >94%) due to COVID-19 were consecutively evaluated.

2.2. Pharmaceutical interventions

In accordance with our protocol, all patients with hypoxaemic pneumonia due to COVID-19 were treated with: (i) a third-generation cephalosporin; (ii) oral hydroxychloroquine (HCQ) for 10 days (400 mg twice on the first day, followed by 200 mg twice daily for the next 9 days) in combination with azithromycin (AZT) for 5 days (500 mg on the first day, followed by 250 mg daily for the next 4 days) in the absence of contraindications and if the symptoms lasted <10 days; and/or (iii) corticosteroids, if >3 L/min of oxygen was required 8 days after the onset of symptoms (1 mg/kg/day the first week, followed by 0.5 mg/kg/day for the next 2 weeks). Patients were not treated with HCQ/AZT if they did not require oxygen therapy.

2.3. Statistical analysis

Results are expressed as total number (%) for categorical variables and as the median (interquartile range) for continuous variables. Continuous variables were compared using the non-parametric Wilcoxon–Mann–Whitney test, and categorical variables were compared using Fisher's exact test. A *P*-value of <0.05 was considered statistically significant. Analyses were conducted using SPSS 15.0 (SPSS Inc., Chicago, Il, USA).

3. Results

Over the study period, 398 patients tested positive for COVID-19 in Réunion Island, with 285 cases (71.6%) imported from Europe. A total of 164 patients were hospitalised, of whom 36 (22.0%) developed hypoxaemic pneumonia. The median time from onset of symptoms to diagnosis of hypoxaemic pneumonia was 5.5 (3.8–8) days.

HCQ/AZT treatment was initiated in 23 (63.9%) of the 36 patients 8 (6–9.5) days after the onset of symptoms. HCQ/AZT treatment was initiated with a median delay of 2 (1–3) days after the diagnosis of hypoxaemic pneumonia. Of these, 17 patients were treated in a medical ward.

Among the 13 hospitalised patients with hypoxaemic pneumonia not treated with HCQ/AZT, 2 were already treated with lopinavir/ritonavir, 7 had symptoms that lasted >10 days and 4 had contraindications.

HCQ/AZT treatment was stopped on Day 4 in 1 patient due to QT prolongation.

Corticosteroid treatment was initiated in 12 patients (33.3%) at a median of 14 (12–15) days after the onset of symptoms, of whom 6 were treated in a medical ward and 6 in the intensive care unit (ICU). Five patients received both HCQ/AZT and corticosteroids.

In the bivariate analysis, HCQ/AZT treatment was associated with a lower rate of ICU admission (P = 0.008) (Fig. 1). Factors predictive of ICU admission (P < 0.05) are shown in Table 1.

Of the 36 patients with hypoxaemic pneumonia, 10 were admitted to the ICU. Of these, four patients received high-flow nasal cannula oxygen therapy (50 L/min of oxygen) and three received invasive mechanical ventilation. Among the 10 patients admitted to the ICU, hospital length of stay was 25 (15–35) days in patients treated with HCQ/AZT and 40 (25–55) days in those not treated with HCQ/AZT (P = 0.3).

One patient under mechanical ventilation was treated with tocilizumab. There were no deaths at follow-up (minimum 60 days). At the time of writing, 163 (99.4%) of the 164 hospitalised patients had been discharged from hospital.

4. Discussion

The evolution of patients was excellent overall, as not a single death due to COVID-19 was reported in Réunion Island. It should be noted, however, that the numbers of COVID-19 cases and hypoxaemic pneumonia cases were relatively low on the island. Several hypotheses can be put forward to explain our results. They may be due to the care bundle used for the management of patients with COVID-19 in Réunion Island. The main intervention was early treatment with HCQ/AZT. Indeed, following bivariate analysis, HCQ/AZT treatment was associated with a lower rate of ICU admission (P = 0.008). Some studies suggest that this drug combination is associated with a decrease in viral load and improved prognosis when administered early [2,3]. It should be noted, however, that HCQ/AZT treatment was not associated with better outcomes in some retrospective studies [4]. Likewise, administration of corticosteroids to patients with no improvement 8 days after the onset of symptoms may have contributed to the favourable outcome of patients with COVID-19 (none of the six patients treated with corticosteroids were hospitalised in the ICU). One study has found corticosteroid treatment to be associated with decreased mortality in patients with hypoxaemic pneumonia due to COVID-19 [5].

This study has many limitations. This was a retrospective study with a relatively small number of patients, which made it impossible to perform multivariate analyses. Despite the risk profile of COVID-19 patients with severe hypoxaemic pneumonia, the mortality rate of the disease in Réunion Island was 0%. This may

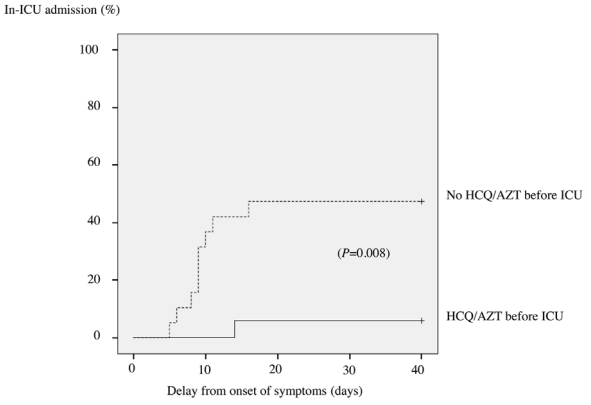

Fig. 1. Kaplan–Meier survival curves: intensive care unit (ICU) admission between patients treated and not treated with hydroxychloroquine/azithromycin (HCQ/AZT).

Table 1
Characteristics at hospital admission of patients with hypoxaemic pneumonia due to COVID-19.

Characteristic	Total (n = 36)	ICU admission		P-value
		No (n = 26)	Yes (n = 10)	
Delay between diagnosis and onset of symptoms (days)	5.5 (2.5–7)	6 (2.5–7)	5 (4–6.8)	0.82
Oxygen therapy (L/min)	3 (1.8–4)	2 (1–3)	6 (8–4.2)	<0.0001
Male sex	25 (69.4)	15 (57.7)	10 (100)	0.02
Age (years)	66 (56–77)	63 (57–75)	71 (59–74)	0.61
Hypertension	12 (33.3)	6 (23.1)	6 (60)	0.05
Diabetes mellitus	5 (13.9)	2 (7.7)	3 (30)	0.12
Body mass index >30 kg/m^2	6 (16.7)	4 (15.4)	2 (20)	0.43
Chronic kidney disease	3 (8.3)	0	3 (30)	0.02
Chronic obstructive pulmonary disease	10 (27.8)	7 (26.9)	3 (30)	0.58
Cardiovascular disease	8 (22.2)	6 (23.1)	2 (20)	0.41
Tobacco smoking (current or former)	11 (30.6)	7 (26.9)	4 (40)	0.69
Renin–angiotensin system inhibitor	8 (22.2)	5 (19.2)	3 (30)	0.66
Leukocyte count ($\times 10^9$/L)	5.6 (4.2–9.8)	5.1 (4–6.9)	9.3 (6.1–13.7)	0.02
Polynuclear neutrophils ($\times 10^9$/L)	3.3 (2.3–6.6)	3.2 (2.5–5)	7.9 (4.1–12.3)	0.02
Lymphocyte count ($\times 10^9$/L)	1.2 (0.85–1.49)	1.2 (0.9–1.6)	0.9 (0.5–1.2)	0.03
D-dimer level (μg/mL)	0.83 (0.51–1.33)	0.62 (0.51–1.19)	1.16 (0.88–3.92)	0.15
Prothrombin time (%)	79 (68–93)	83 (70–93)	72 (67–81)	0.36
C-reactive protein (mg/dL)	74 (18–113)	97 (17–89)	129 (76–160)	0.02
Cardiac troponin I > 10 ng/L	8 (22.2)	2 (9.1)	6 (60)	0.005
Lactate dehydrogenase (IU/L)	376 (285–429)	334 (259–428)	377 (331–407)	0.57
Glomerular filtration rate (mL/min)	87 (66–95)	88 (71–95)	69 (51–93)	0.21
Pulmonary infiltrates >50% extension on chest CT	11 (30.6)	4 (15.4)	7 (70)	0.003
Lopinavir/ritonavir started before ICU admission	2 (5.6)	0	2 (20)	0.07
Corticosteroids started before ICU admission	6 (16.7)	6 (23.1)	0	0.16
HCQ/AZT started before ICU admission	17 (47.2)	16 (61.5)	1 (10)	0.008

NOTE: Results are expressed as n (%) or median (interquartile range) as appropriate.
COVID-19, coronavirus disease 2019; ICU, intensive care unit; CT, computed tomography; HCQ/AZT, hydroxychloroquine/azithromycin.

be due to the care bundle used in our hospital (early hospitalisation, treatment with HCQ/AZT and/or corticosteroids, non-invasive respiratory support, etc.).

Availability of data and material

The data set used in the current study is available from the corresponding author on reasonable request.

Funding

None.

Competing interest

None declared.

Ethical approval

This observational study was approved by the Ethics Committee of the French Society of Pulmonary Medicine and was declared to the Commission nationale de l'informatique et des libertés (French Data Protection Agency or CNIL MR004) [No. 2,206,739]. Written and verbal informed consent was obtained from all patients.

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