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Original article

Successful high flow nasal cannula therapy for severe COVID-19 pneumonia is associated with tocilizumab use

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ABSTRACT

Introduction: Our aim was to determine the rate of success of HFNO and its relationship with current treatments for severe COVID-19.
Method: This was a cohort study including patients admitted for HFNO because of respiratory failure despite oxygen therapy through a facial mask. Care was standardized, with systematic use of steroids and prevention or treatment of thromboembolic complications, and tocilizumab when deemed useful. HFNO failure was defined by the requirement for mechanical ventilation and/or death.
Results: In August 2021, among 1397 patients with COVID-19 admitted in the emergency department, 110 (7.8%) received HFNO (mean age 55 years, sex-ratio M/F 1.4). Thirteen patients (12%) had received a steroid treatment before hospital admission. At least one comorbid condition was observed in 57% of the patients. Mean duration of the disease at admission was 8.8 days and mean respiratory rate was 34/min. A CT scan was performed for 101 patients (92%), among whom 13 had a pulmonary embolism. All patients received a steroid treatment, and tocilizumab was prescribed in 79 cases (72%). Failure of HFNO was observed in 54 cases (49%); the only risk factor was the absence of tocilizumab administration: AOR [IC95%] 3.50 [1.40-8.69]. We observed a trend toward failure with steroid use before hospital admission: AOR 3.83 [0.96-16.66].
Conclusion: Success of HFNO, when all therapeutic means of treatment for severe COVID-19 pneumonia were applied, was associated with tocilizumab administration. Our data suggest the interest of a randomized study to determine whether HFNO is the right signal for prescription of anti-IL6 drugs.

1. Introduction

The current pandemic of COVID-19 infections has led to successive waves of cases, depending on several factors such as host immunity, viral variant, and the characteristics of the circulating variant [1,2]. The main organ targeted by the SARS-Cov-2 is the pulmonary tract, potentially leading to respiratory failure, especially in elderly patients and/or those with multiple comorbid conditions, including immunosuppression [2,3].

The high frequency of patients with respiratory failure due to COVID-19 has led to proposals to use of high flow nasal cannula oxygen therapy (HFNO) in order to avoid intensive care unit (ICU) admission for mechanical ventilation [3–7]. This modality of oxygen therapy is demonstrably d more efficient than standard oxygen therapy using facial masks, for hypoxic respiratory failure related to acute community-acquired infections [8]. Successive studies have shown the benefit of HFNO, as 45 to 70% of the patients with respiratory failure due to COVID-19 did not require mechanical ventilation [3–7]. As a result, it is now widely accepted that HFNO is an adequate tool for respiratory failure due to COVID-19.

Surprisingly, these studies have not included in their analyses the impact of steroids and/or anti-interleukine-6 drugs such as tocilizumab or sirulimab, which have been proposed in cases of severe COVID-19 pneumonia, even though the right time for the administration of these anti-inflammatory compounds is still debated [5,9–12]. Moreover, in spite of the fact that these studies on HFNO efficacy have included patients with severe forms of the disease, there has been no report on the rate of pulmonary embolism and associated preventive or curative treatment, as well as other complications observed during COVID-19, which may influence the outcome [13,14]. Therefore, our aim was to determine the rate of real-life HFNO success in a major wave of COVID-19 with overcrowded ICUs, in which anti-inflammatory drugs as well as other standard of care therapeutic means were administered in medical wards to patients with respiratory failure.

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2. Method

This is a retrospective cohort study conducted in the University Hospital of Guadeloupe (Pointe-à-Pitre, French West Indies), the reference hospital of the island for COVID-19. All adult patients (>18 years old) included were hospitalized in our 18-bed dedicated ward for a severe form of confirmed SARS-CoV2 infection, defined by a failure of oxygen therapy using a facial mask and consequently necessitating HFNO.

RNA detection of SARS-CoV-2 was assessed by RT-PCR on nasopharyngeal swab. Patients initially hospitalized in intensive care unit (ICU) were excluded. All positive samples were screened for Delta variant in a reference lab (Institut Pasteur, Paris, France).

Comorbidities were defined by their specific treatments prescribed to the patient before hospital care, or if the diagnosis was newly established during the hospital stay.

2.1. Ethics

The protocol was approved by the local ethics committee and patients were included in the database "French COVID" (recording center 050). All sociodemographic, clinical, laboratory and outcomes data were extracted from the patients' electronic medical files. The therapeutic audits were sponsored by the French National Health Agency, and the patients or their relatives provided written consent for computerization of their anonymized personal data for hospitalization according to the French national ethics recommendations.

2.2. Standard of care for Covid-19 in our hospital

A treatment with corticosteroids before hospital admission was systematically reported, because in the context of the large-scale wave of COVID-19 in Guadeloupe, family practitioners were prescribing these compounds in ambulatory care.

Hospitalized patients were treated following institutional protocols. Parenteral dexamethasone was the single steroid therapy used (6 mg qd) for at least 3 days, followed by oral prednisolone (40 mg qd) to complete a total of 10 days of steroid therapy. In the absence of improvement after 24 to 36 hours, tocilizumab was added with a single infusion of 8 mg/kg (maximal dose of 800 mg). Tocilizumab could also be administered concomitantly to dexamethasone when HFNO was started immediately with $FiO_2 > 60\%$.

As the efficacy of the treatments for respiratory failure may be associated with the precocity of their administration, we calculated the time interval between the onset of the symptoms and the outset of the treatment.

In the absence of renal insufficiency (defined by creatinine clearance < 30 ml/min), prevention of thrombo-embolism was attempted using enoxaparine, of which the dosage was related to weight. In case of severe renal insufficiency, calciparine was used [13]. All patients were hydrated with intravenous fluids, had insulin therapy in case of diabetes and were administered gastric ulcer prevention with lansoprazole. We systematically searched for any acute organ failure related to SARS-CoV-2 infection, including cardiac event, acute kidney injury and neurologic disorders [14–16].

CT scan analysis was performed respecting the guidelines of the French Society of Thoracic Imaging [17].

High flow nasal cannula (Airvo2, Fisher-Paykel Healthcare) was usually started with an oxygen flow rate of 40 l/min and FiO2 of 60%, humidified and heated to 28–32 °C. Failure of HFNO was defined by required mechanical ventilation and/or death, with clinical follow-up until hospital discharge.

2.3. Statistical analysis

The data were analyzed with StatView software version 5.0, and statistical significance was established at $\alpha = 0.05$. The continuous variables were compared with the Student's *t*-test or the Mann-Whitney test when appropriate. Proportions were compared with the χ^2 or Fisher's exact test when appropriate. Logistic regression was used to study the risk factors of HFNO failure, and the results are presented as adjusted odds ratios (AORs) with

Table 1
Characteristics of the 110 patients with severe COVID-19 pneumonia treated by HFNO with or without tocilizumab. It should be noted that all patients had received steroid therapy.

Characteristics	Total *n* = 110 (100%)	Tocilizumab treatment *n* = 79 (72%)	Without tocilizumab *n* = 31 (28%)	*P*
Sex-ratio (M/F)	1.43	1.32	1.38	0.916
Age (years)	55 ± 11	53 ± 11	61 ± 10	<0.001
Underlying conditions				
At least one comorbid condition	63 (57)	44 (56)	19 (61)	0.593
Diabetes	30 (27)	19 (24)	11 (35)	0.225
Hypertension	52 (47)	35 (44)	17 (55)	0.319
Obesity	50 (45)	38 (48)	12 (39)	0.373
Pulmonary disease	11 (10)	10 (13)	1 (3)	0.137
Other comorbid conditions[1]	7 (6)	4 (5)	3 (10)	0.647
Duration of symptoms before admission	8.8 ± 3.3	8.9 ± 3.2	8.6 ± 3.6	0.433
Respiration rate on admission (/min)	34 ± 8	33 ± 8	36 ± 9	0.138
Chest CT scan on admission	101 (92)	74 (94)	27 (87)	0.456
Lung affected ≤ 25%	35 (35)	23 (31)	12 (44)	0.228
Lung affected 26-50%	51 (51)	38 (52)	13 (48)	0.528
Lung affected > 50%	14 (14)	12 (16)	2 (7)	0.69
Pulmonary embolism	13/101 (13)	5/54 (9)	8/47 (17)	0.245
C-reactive protein (mg/L) on admission	145 ± 79	144 ± 76	148 ± 87	0.878
Treatment				
Duration of symptoms at HFNC initiation	10.4 ± 3.5	10.6 ± 3.3	9.9 ± 4.0	0.295
Corticosteroids before hospital admission	13 (12)	8 (10)	5 (16)	0.38
Other complications due to Covid-19	30 (27)	21 (26)	9 (29)	0.795
Acute kidney injury	12 (11)	8 (10)	4 (13)	
Cardiac complications	10 (9)	9 (11)	1 (3)	0.004
Pulmonary bacterial superinfection	6 (5.4)	2 (2.5)	4 (1.3)	0.124
Neurologic involvement	2 (1.8)	2 (2.5)	0	
Outcome				
HFNO failure	54 (49)	32 (41)	22 (71)	
death	31 (28)	19 (24)	12 (39)	

Values are expressed in n (%), or mean ± std deviation.

Table 2
Risk factors for unfavourable outcome of patients with severe COVID-19 pneumonia treated by HFNO. An unfavorable outcome was defined as mechanical ventilation requirement and/or death. A total of 31 patients (28%) died during hospitalization.

Characteristics	Favourable Outcome $n = 56$ (51%)	Unfavourable Outcome $n = 54$ (49%)	P	AOR [CI 95%]
Age (years)	53 ± 11	58 ± 11	0.014	
Sex-ratio (M/F)	1.8	1	0.13	
Underlying conditions				
At least one comorbid condition	30 (54)	33 (61)	0.639	
Diabetes	15 (27)	15 (28)	0.907	
Hypertension	24 (50)	28 (57)	0.344	
Obesity	28 (50)	22 (41)	0.329	
Pulmonary disease	6 (11)	5 (9)	0.799	
Other comorbid conditions[1]	4 (7)	3 (6)	0.733	
Duration of symptoms before admission	9.1 ± 3.2	8.6 ± 3.4	0.613	
Respiration rate on admission (/min)	36 ± 9	33 ± 7	0.234	
Chest CT scan on admission	54 (96)	47 (87)	0.072	
Lung affected ≤ 25%	19 (36)	16 (34)	0.85	
Lung affected 26–50%	28 (53)	23 (49)	0.697	
Lung affected > 50%	6 (11)	8 (17)	0.412	
Pulmonary embolism	5/54 (9)	8/47 (17)	0.245	
Biological data on admission				
C-reactive protein (mg/L)	149 ± 78	141 ± 79	0.463	
Treatment				
Duration of symptoms at HFNC initiation	10.9 ± 3.5	9.9 ± 3.6	0.221	
Corticosteroids before hospital admission	3 (5)	10 (19)	0.032	3.83 [0.96–16.66]
Glucocorticoids	56 (100)	54 (100)	–	
Tocilizumab	47 (84)	32 (59)	0.004	3.50 [1.40–8.69]
Administered concomitantly to steroids	33/47 (70)	24/32 (73)	0.641	
Other complications due to Covid-19	15 (26)	15 (28)	0.907	
Cardiac complications	7 (12)	3 (6)		
Acute kidney injury	3 (5)	9 (17)		
Pulmonary bacterial superinfection	3 (5)	3 (6)		
Neurologic involvement	2 (4)	0		

Other comorbid conditions include: congestive heart failure ($n = 5$), renal graft ($n = 1$), chronic lymphoid leukemia ($n = 1$). Values are expressed in n (%), or mean ± std deviation. AOR: adjusted odds ratio.

their 95% confidence intervals (CIs). Variables were selected for the multivariate analysis based on the level of significance of the bivariate association with HFNO failure ($P < 0.2$). Models were built up sequentially, starting with the variable most strongly associated with HFNO failure and continuing until no other variable reached significance or altered the odds ratios of variables already in the model. When the final model was reached, each variable was dropped, one by one, to assess its effect.

3. Results

In August 2021, 1397 patients with COVID-19 were admitted in our emergency department, among whom 110 (7.8%) received HFNO. During this fourth wave of COVID-19 in Guadeloupe, all cases were related to the Delta variant of SARS-CoV-2. Mean age was 55 years, and sex-ratio M/F was 1.4 (see Table 1). Steroid therapy was prescribed for 13 patients (12%) before hospital admission. More than half of the patients had at least one comorbid condition and all patients had a high rate of respiration [median 33/min, range (20–60)]. Chest CT scan ($n = 101$) showed pulmonary embolism in 13 patients. COVID-19 also led to other organ dysfunctions, including acute renal failure ($n = 12$), cardiac events ($n = 10$), bacterial superinfection ($n = 6$) and neurologic involvement ($n = 2$).

All patients received dexamethasone, and 79 patients (72%) were given tocilizumab. The main characteristics of patients with or without the latter drug are detailed in Table 1. The patients receiving tocilizumab were younger (53 vs. 61 years, $P < 0.001$), but the other parameters, i.e. comorbid conditions and severity, were comparable compared to patients not receiving this drug.

HFNO failure was observed in 54 cases (49%), with a median time of 3.3 ± 2.7 days. There were 40 mechanical ventilation requirements, and 11 deaths in our department. Ultimately, 31 patients (28%) died during hospitalization. HFNO duration for the patients with favorable outcome was 6.5 ± 3.5 days.

Using logistic regression, pulmonary embolism and other complications related to COVID-19 were not risk factors for unfavorable outcome (see Table 2). The only risk factor associated with the latter was the absence of tocilizumab prescription with an adjusted odds ratio [95% CI] of 3.50 [1.40–8.69] ($P = 0.007$). We also observed a trend toward an unfavourable outcome and prescription of a steroid therapy before hospital admission (AOR [95% CI]: 3.83 [0.96–16.66] ($P = 0.057$).

4. Discussion

Our cohort study shows that in the context of a wave of the SARS-CoV-2 Delta variant, half of the patients with respiratory failure admitted for HFNO in a dedicated unit had a favourable outcome without need for mechanical ventilation. Moreover, the administration of tocilizumab was associated with a favourable outcome in patients receiving HFNO therapy, considering that all patients had also received corticosteroids. Finally, we observed a trend toward an association between steroid therapy before hospital admission and unfavourable outcome of HFNO therapy.

Our study has some limitations. First, this was a retrospective monocentric cohort study in Guadeloupe, an overseas department of France in the Caribbean. However, it is hard to build a study in conjunction with other centres, when the COVID-19 waves do not simultaneously occur in different territories, and do not have the same impact on the public health service. Second, our internal guideline suggested initiation of tocilizumab at the prescriber's discretion, leading to the fact that nearly one third of the patients did not receive this compound. However, Table 1 shows that only a minor difference of age (8 years) was observed between patients receiving this drug and the others, and from our point of view this difference is without major clinical relevance for patients with severe COVID-19 pneumonia necessitating HFNO.

Our success rate of HFNO (51%) was in a range comparable to previous studies: 47% in a South African study including

293 patients, and 71.4% in a Mexican cohort study including 270 patients [3,4]. Of note, in these two studies, one third of the patients did not receive steroid therapy, and none received tocilizumab. The first explanation for the low success rate of HFCO to avoid mechanical ventilation and/or death despite quasi-systematic use of anti-inflammatory drugs is that we were facing a heavy wave of the SARS-CoV-2 Delta variant in a poorly vaccinated population (less than 20% of fully vaccinated adults at the beginning of the wave in August 2021). As viral excretion of this variant is higher compared to previous ones, it could also be more pathogenic, and the anti-inflammatory drugs used to reduce the cytokine storm might be less efficient [18]. The second hypothesis is that patients feared coming to the hospital, as they feared the vaccines against SARS-CoV-2, and therefore came to the hospital very late. This could also explain the high rate of patients (12%) who received steroid therapy before admission, probably delaying their hospital admission. Indeed, these patients had a higher disease duration before hospital admission (11.8 ± 2.9 vs. 8.4 ± 3.2 days, $P < 0.001$) and radiological pulmonary involvement > 50% on CT-scan (33% vs. 11%, $P = 0.039$) was more frequent.

Our study shows a relationship between tocilizumab prescription and a favourable outcome for patients with severe COVID-19 pneumonia. Very few studies have focused on the benefit of tocilizumab and steroids in this patient population. In a study including 125 patients treated with dexamethasone and tocilizumab, compared to 59 patients treated with tocilizumab alone, the death rates were 22.4 vs. 6.8% respectively [19]. However, fewer than 10% of the patients required HFNO. In another study in which corticosteroids were administered in almost all patients (93%), tocilizumab was associated with reduced disease progression in 42/50 cases (84%) compared to 27/41 cases (66%) without this drug ($P = 0.044$) [11]. Consequently, our study may help to identify the patients who could derive maximal benefit from tocilizumab, with the initiation of HFNO being a good signal for its prescription.

Finally, our study underlines a trend toward a relationship between steroid prescription by family practitioners and an unfavourable outcome after hospital admission. We have emphasized this trend because the fourth wave in Guadeloupe was dramatic, overstretching hospital resources, and corticosteroid prescription in ambulatory care of oxygen-dependant Covid-19 patients became very frequent. This suggests that ambulatory management should be carefully evaluated in the future.

5. Conclusion

A better outcome of HFNO in cases of severe COVID-19 pneumonia was associated with tocilizumab prescription. Consequently, the signal for anti-IL6 drug administration could consist in HFNO requirement. Our data argue for a randomised prospective study.

Ethics approval

The audit was sponsored by the French National Health Agency; the patients or their relatives provided written consent for computerization of their personal data for hospitalization purposes and clinical research. In accordance with national directives, patient privacy was protected as no personal data were extracted or copied from the computerized chart.

Availability of data and material

The data used during the current study are available from the corresponding author on reasonable request

Code availability

StatView software version 5.0.

Consent for publication

All authors have read the paper and consent to its publication

Funding source

None; this study was carried out as part of our routine work.

Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

R.O., P-M.R. contributed to the study design. P-M.R. R.O. contributed to the statistical analysis; R.O., P-M.R., E.C., M.B., C.L.G., I.F. and S.M. contributed to the writing of the article; R.O., E.C., M.B., C.L.G., I.F. contributed to the study design and patient inclusion.

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