Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine.

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The current outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) represents a source of concern for the management of patients with systemic lupus erythematosus (SLE). Indeed patients with SLE have an increased risk of severe infections due to intrinsic perturbations of their immune response, the use of immunosuppressive drugs, as well as the potential presence of organ damage associated with their disease. In this context, hydroxychloroquine (HCQ), a drug that is currently part of the long-term, standard-of-care treatment for SLE, has been reported to possess antiviral activity in vitro, and recent results from a preliminary clinical trial might support its use in curative or even prophylactic treatment for COVID-19.[1–3]

During the first days of the COVID-19 outbreak in France, we launched an observational study with the aim to follow the clinical course of COVID-19 in patients with SLE who received long-term treatment with HCQ. To be eligible, patients with SLE had to (1) fulfil the 1997 criteria of the SLE classifications of the American College of Rheumatology or those of the 2019 European League Against Rheumatism/American College of Rheumatology[4 5]; (2) be on long-term treatment with HCQ; and (3) have SARS-CoV-2 carriage in their nasopharyngeal swab, as confirmed by real-time reverse transcription PCR analysis.

Data were collected from 17 patients with SLE between 29 March and 6 April (tables 1 and 2). The initial symptoms of the first patient appeared on 5 March and those of the last patient on 26 March. The main comorbidities were obesity and chronic kidney disease, which were present in 10 (59%) and 8 (47%) patients, respectively. All patients except one had clinically quiescent SLE, defined as a clinical Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score equal to 0.[6] The duration of HCQ treatment prior to COVID-19 was relatively long, with a median (range) of 7.5 (0.5–29.8) years. Twelve (71%) patients were also treated with prednisone, at doses usually below 10 mg per day, and seven (41%) with an immunosuppressant. Except for a higher rate of dyspnoea, headache and diarrhoea, clinical signs and symptoms of COVID-19 were similar to those described previously.[7 8]

Viral pneumonia was diagnosed in 13 (76%) patients, with complications due to respiratory failure in 11 (65%) and acute respiratory distress syndrome in 5 (29%). Three patients suffered from acute renal failure, with two patients requiring haemodialysis. At admission, HCQ and prednisone were maintained at the same dose, whereas immunosuppressant drug intake was interrupted or decreased. HCQ blood concentrations were assessed in eight patients at admission or during hospitalisation. Its median (range) was 648 (254–2095) ng/mL. No additional antiviral treatments were started. Antibiotics were administered in nine (53%) cases even though no bacterial infections, except in one case, were documented. A total of 14 (82%) patients were admitted to hospital care, including 7 (41%) to an intensive care unit. Oxygen therapy was given to 11 (65%) patients, requiring nasal cannula in 5, high-flow nasal cannula in 1 and invasive mechanical ventilation in 5. One patient was treated with extracorporeal membrane oxygenation. As of 7 April, five (36%) patients have been discharged from the hospital, seven (50%)

Table 1 Demographics and baseline characteristics of patients with SLE infected with SARS-CoV-2

	Patients (N=17)
Women	13 (76)
Age, years, median (range)	53.5 (26.6–69.2)
SLE	16 (94)
Lupus-like syndrome*	1 (6)
Antiphospholipid syndrome	4 (24)
Disease duration, years, median (range)	8.2 (0.8–42.7)
SLICC Damage Index	1 (0–8)
Chronic medical illness	
Cerebrovascular disease	3 (18)
Coronary heart disease or cardiovascular disease	2 (12)
Diabetes	0 (0)
Body mass index	
Normal (18.5–25)	5 (29)
Overweight (25–30)	2 (12)
Obesity (≥30)	10 (59)
Hypertension	6 (35)
Malignant tumour	1 (6)
Nervous system disease	1 (6)
Chronic obstructive lung disease	2 (12)
Chronic kidney disease	8 (47)
Chronic kidney disease staging	
Mildly decreased (GFR MDRD 89-60 mL/min/1.73 m^2)	3 (18)
Mildly to severely decreased (GFR MDRD 59–30 mL/min/1.73 m^2)	2 (12)
Severely decreased (GFR MDRD 29–15 mL/min/1.73 m^2)	0 (0)
Kidney failure (GFR MDRD <15 mL/min/1.73 m^2)	3 (18)
Smoking habits	
Never smoker	10 (59)
Ex-smoker	5 (29)
Daily smoker	2 (12)
History of thrombosis	6 (35)
Arterial thrombosis	3 (18)
Venous thrombosis	4 (24)
Current or history of:	
Arthritis	14 (82)
Mucocutaneous involvement	10 (59)
Lupus nephritis	9 (53)
Serositis	9 (53)
Cytopaenia	6 (35)
Neuropsychiatric lupus	4 (24)
Treatment regimen	
HCQ 200 mg/day	4 (24)
HCQ 400 mg/day	11 (65)
HCQ >400 mg/day	2 (12)
Duration of HCQ treatment, years, median (range)	7.5 (0.5–29.8)
Prednisone use	12 (71)
Prednisone ≥10 mg per day	2 (12)
Immunosuppressive agent use†	7 (41)
ACE inhibitors and/or ARBs	6 (35)
Non-steroidal anti-inflammatory drugs	0 (0)
Oral anticoagulant‡	5 (29)
SLE activity	
Clinical manifestation of SLE	1 (6)
Positive anti-dsDNA test	6 (35)

Continued

Table 1 Continued

	Patients (N=17)
Low C3	2 (12)

Values are expressed as n (%), unless stated otherwise.
*Patients who fulfilled only 2–3 1997 American College of Rheumatology criteria for SLE were classified as antiphospholipid syndrome (APLS) associated with lupus-like syndrome.
†Excluding antimalarials and prednisone. Immunosuppressant therapy was mycophenolate mofetil for five patients and methotrexate for two.
‡Oral anticoagulant was warfarin for three patients, fluindione for one and rivaroxaban for one.
ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; dsDNA, double-stranded DNA antibodies; GFR, glomerular filtration rate; HCQ, hydroxychloroquine; MDRD, Modification of Diet in Renal Disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; SLICC Damage Index, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

remained hospitalised and two (14%) died. Except for a single patient with active tenosynovitis at the onset of SARS-CoV-2 infection, none of the patients showed clinical signs of lupus during COVID-19.

This case series does not allow to draw conclusions on the incidence rate and severity of COVID-19 in SLE. However, it gives a first clinical picture of the course of this infection in patients with SLE treated with HCQ, and it furthermore paves the way for a larger observational study to identify the risk factors associated with the occurrence of a severe form of COVID-19 in patients with SLE. With a high prevalence of comorbidities such as chronic kidney disease and obesity, patients with SLE could suffer from severe forms of COVID-19.[9 10] In patients with SLE with chronic renal disease, besides the risk of respiratory failure, the danger of acute renal failure should be considered as well.

At present, we are awaiting the results of the European Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy, NCT04315948), which has the primary objective of evaluating the clinical efficacy and safety of different investigational therapeutics, including HCQ. Notwithstanding, our preliminary conclusion, based on the observation that most of the patients with SLE in this study received long-term treatment with HCQ, having blood concentrations of the drug within therapeutic range, is that HCQ does not seem to prevent COVID-19, at least its severe forms, in patients with SLE.

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Table 2 Clinical characteristics, laboratory results, treatment and outcome of patients with SLE infected with SARS-CoV-2

	Patients (N=17)
Signs and symptoms at baseline	
Fever	17 (100)
Cough	14 (82)
Sputum	4 (24)
Shortness of breath	14 (82)
Respiratory rate >24 breaths per minute	9 (53)
Pulse >125 beats per minute	3 (18)
Myalgia	8 (47)
Confusion	1 (6)
Headache	10 (59)
Sore throat	6 (35)
Rhinorrhoea	4 (24)
Dysgeusia	5 (29)
Anosmia	5 (29)
Chest pain	4 (24)
Diarrhoea	7 (41)
Nausea and/or vomiting	3 (18)
Fever + cough + shortness of breath	13 (76)
Time from illness onset to fever, days	0 (0–12)
Time from illness onset to cough, days	2.5 (0–12)
Time from illness onset to dyspnoea, days	4 (0–14)
Time from illness onset to ARDS, days	8 (3–13)
Final diagnosis and comorbid conditions	
Upper respiratory tract infection	9 (53)
Pneumonia	13 (76)
Respiratory failure	11 (65)
ARDS	5 (29)
Acute cardiac injury*	1 (6)
Acute renal injury	3 (18)
Septic shock	2 (12)
Ventilator-associated pneumonia	0 (0)
Other secondary infection	1 (6)
Venous thrombosis	1 (6)
Chest CT finding: extension of GGO and/or consolidation†	
<10%	1/10 (10)
10%–25%	3/10 (30)
25%–50%	3/10 (30)
>50%	3/10 (30)
Treatment	
Hydroxychloroquine	
Maintenance	17 (100)
200 mg/day	5 (29)
400 mg/day	9 (53)
>400 mg/day	3 (18)
Whole-blood HCQ concentrations, ng/mL, median (range)‡	648 (254–2095)
Prednisone	
Maintenance	12/12§ (100)
Increase or start of prednisone	0 (0)
Immunosuppressant	
Withdrawal or decrease of usual immunosuppressant	6/7§ (86)
Introduction of tocilizumab	1 (6)
Antiviral therapy	0 (0)
Antibiotic therapy¶	9 (53)
Oxygen therapy	11 (65)
Nasal cannula	5/11 (45)

Continued

Table 2 Continued

	Patients (N=17)
Non-invasive ventilation or high-flow nasal cannula	1/11 (9)
Invasive mechanical ventilation	5/11 (45)
ECMO	1 (6)
Prognosis	
Admission to hospital	14 (82)
Admission to intensive care unit	7 (41)
Clinical outcome	
Discharged	5/14** (36)
Remained in hospital	7/14** (50)
Died	2/14** (14)

Values are expressed as n (%), unless stated otherwise.
*Defined as new abnormalities shown on echocardiography.
†Ten patients were assessed.
‡Eight patients were assessed at admission or during the hospitalisation.
§Number of patients under this treatment regimen.
¶Including azithromycin for two patients and spiramycin for two other patients.
**Number of patients hospitalised.
ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; GGO, ground-glass opacities; HCQ, hydroxychloroquine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus.

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Patient consent for publication Patients were informed that data collected in medical records might be used for research study in accordance with privacy rules.

Ethics approval This observational study was based on data extracted from medical records, in strict compliance with the French reference methodology MR-004, established by the French National Commission on Informatics and Liberty (CNIL), in accordance with the French law, including the GPRD. This study was approved by the Research Ethics Committee of Sorbonne University (CER-2020-12).

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REFERENCES

1 Savarino A, Boelaert JR, Cassone A, *et al*. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* 200:722–7.
2 Gautret P, Lagier J-C, Parola P, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:10949.
3 Spinelli FR, Ceccarelli F, Di Franco M, *et al*. To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic. *Ann Rheum Dis* 2020;79:666–7.
4 Hochberg MC. Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:40.
5 Aringer M, Costenbader K, Daikh D, *et al*. 2019 European League against Rheumatism/American College of rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:1151–9.
6 van Vollenhoven R, Voskuyl A, Bertsias G, *et al*. A framework for remission in SLE: consensus findings from a large international Task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017;76:554–61.
7 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
8 Chen N, Zhou M, Dong X, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
9 Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
10 ICNARC. Report on 2249 patients critically ill with COVID-19, 2020. Available: https://www.icnarc.org/DataServices/Attachments/Download/76a7364b-4b76-ea11-9124-00505601089b