Systematic analysis of COVID-19 infection and symptoms in a systemic lupus erythematosus population: correlation with disease characteristics, hydroxychloroquine use and immunosuppressive treatments

We read with interest the article of Bozzalla Cassione *et al* about COVID-19 incidence in their systemic lupus erythematosus (SLE) cohort.[1] Their study adds useful epidemiological information about COVID-19 risk in SLE.[1] They suggest that hydroxycholoroquine was not protective, but could not draw definite conclusion and open the question to immunosuppressive drugs' influence. We would like to share analysis of our SLE cohort (n=225) that can help to answer these questions and determine COVID-19 infection risk factors.

Determining COVID-19 incidence is challenging: PCR lacks sensitivity, was usually realised only in severely ill patients and patients with suggestive benign symptoms could stay at home without medical contact. We studied the incidence of COVID-19 infection, either asserted or suspected, by analysing positive nasopharyngeal PCR, hospitalisation or contact with emergency department, but also suspected diagnosis in ambulatory medicine. Each patient was called by phone to determine COVID-19 suggestive symptoms since 4 February 2020, date of the first case in our country.

Among our patients, 92.9% were female, with a mean (±SD) age of 51.7 (±14.9) years. Most recent biological evaluation showed positivity for ds-DNA in 24% (median (min–max) levels: 139 (12–758) IU/mL). Mean (±SD) number of 1997 American College of Rheumatology (ACR), 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) and Systemic Lupus International Collaborating Clinics (SLICC) classification criteria were 4.5 (±1.5), 20.0 (±8.1) and 5.8 (±2.2), respectively. One hundred and fifty-two (68.1%) patients received chronic treatment with hydroxychloroquine, while 92 (42.4%) had an immunosuppressive treatment (glucocorticoid: 25.3%; other immunosuppressive drug: 31.4%). Mean (±SD) glucocorticoid dose was 4.2 (±2.9) mg of methylprednisolone. Immunosuppressive drugs were ledertrexate (n=23, 10.2%), mycophenolate/tacrolimus/everolimus (n=21, 9.3%), azathioprine (n=25, 11.1%), belimumab (n=5, 2.2%) and rituximab (n=3, 1.3%).

In our cohort, a high suspicion of COVID-19 infection was not uncommon, but with absence of severity. Infection was confirmed or suspected by medical team in 18 (8.0%) patients (table 1): 5 (2.2%) had a positive PCR; 7 (3.1%) were admitted to emergency department (without hospitalisation) and 2 (0.9%) were hospitalised (without intensive care unit, while 1 for the Italian cohort[1]) with COVID-19 infection suspected or confirmed by the medical team; and 14 (6.2%) were highly suspected of COVID-19 after a medical appointment in ambulatory medicine. COVID-19 suggestive symptoms were listed in table 1: in particular, anosmia/ageusia were declared in 7.6%. The Italian cohort identified a similar rate of positive PCR (2.5%), but a lower rate of COVID-19 suspicion (4.8%): however, they considered a strict definition with association of symptoms and contact with a positive case, while we also declare high clinical suspicion in ambulatory medicine.[1] Another series from New York (NY) estimated the incidence of COVID-19 infection at 2%, but without systematic patient contact[2] and could miss paucisymptomatic patients.

Our data supported the ineffectiveness of chronic use of hydroxychloroquine to prevent COVID-19 disease and symptoms in SLE population, with similar rate of COVID-19 infection or suspicion (infection or suspicion in 12 out of 152 (7.9%) patients treated with hydroxychloroquine, while in 6 out of 73 (8.2%) for patients without, p=0.93) and suggestive symptoms (p=0.97). Patients with hydroxychloroquine were slightly younger (49.7±14.5 years vs 55.6±15.1 years, p=0.0054) but with no difference in terms of gender, biological evaluation, classification criteria, or immunosuppressive and non-rheumatic

Table 1 COVID-19 infection, suspicion and symptoms among patients with systemic lupus erythematosus (n=225)

Variable	Categories	N (Percent)	Variable	Categories	N (Percent)
Dyspnea	No	212 (94.2)	COVID-19 infection confirmed or suspect by medical team	No	207 (92.0)
	Yes	13 (5.8)		Yes	18 (8.0)
Chest pain	No	214 (95.1)	Positive nasopharyngeal PCR	No	220 (97.8)
	Yes	11 (4.9)		Yes	5 (2.2)
Rhinorrhea	No	200 (88.9)	Admission to emergency department (without hospitalization) for COVID-19 symptoms	No	218 (96.9)
	Yes	25 (11.1)		Yes	7 (3.1)
Pharyngeal pain	No	205 (91.1)	Hospitalization for COVID-19 symptoms	No	223 (99.1)
	Yes	20 (8.9)		Yes	2 (0.9)
Cough	No	203 (90.2)	Suspicion of COVID-19 in ambulatory medicine	No	211 (93.8)
	Yes	22 (9.8)		Yes	14 (6.2)
Diarrhea	No	201 (89.3)			
	Yes	24 (10.7)			
Headache	No	191 (84.9)	Ageusia	No	211 (93.8)
	Yes	34 (15.1)		Yes	14 (6.2)
Myalgia	No	209 (92.9)	Anosmia	No	211 (93.8)
	Yes	16 (7.1)		Yes	14 (6.2)
Fever	No	214 (95.1)	Ageusia or anosmia	No	208 (92.4)
	Yes	11 (4.9)		Yes	17 (7.6)
Vomiting	No	220 (97.8)	Ageusia and anosmia	No	214 (95.1)
	Yes	5 (2.2)		Yes	11 (4.9)

treatment, allowing comparison. A French series of 17 SLE patients with COVID-19 infection previously suspected that hydroxychloroquine did not prevent severe form of COVID-19.[3]

The question of immunosuppressive drugs' influence is important because patients could be tempted to stop them. Our data are reassuring: patients under immunosuppressive treatment did not present a higher rate of COVID-19 infection or symptoms (immunosuppressive drug with or without glucocorticoids, with glucocorticoids or without glucocorticoids: p=0.38, p=0.77 and p=0.21, respectively, for infection; p=0.66, p=0.22 and p=0.14, respectively, for symptoms). If each drug was analysed separately, a correlation was found between belimumab and hospitalisation (p=0.04) but only two patients (0.9%) were hospitalised and it was probably without any clinical significance. Classification between 'glucocorticoid use' or 'not' did not reveal any difference in infection (p=0.42) and suggestive symptoms (p=0.89). However, glucocorticoid dose was positively associated with positive PCR (OR 1.57, p=0.025), hospitalisation (OR 4.39, p=0.030), anosmia and ageusia (OR 1.57, p=0.025) and diarrhoea (OR 1.75, p=0.018). This should lead to caution in patients with higher doses of glucocorticoids. Concerns about glucocorticoid chronic use and COVID-19 have emerged: glucocorticoids were associated with prolonged SARS-CoV-2 RNA shedding[4] and were risk factors for hospitalisation in two cohorts of 86 COVID-19-positive patients with inflammatory disease[5] and 600 COVID-19-positive patients with rheumatic disease.[6] Of interest, the patient with SLE described by Bozzalla Cassione *et al* and that needed intensive care unit was under oral prednisolone 7.5 mg/day.[1] Other immunosuppressive treatments were not associated with hospitalisation among the 18 SLE patients with COVID-19 in the NY series.[2]

Characterisation was performed with analysis of classification criteria (positivity and number of criteria), antinuclear antibody (ANA) and ds-DNA levels on the most recent blood analysis available: none had significant influence, underlying that more severe or more active patients with SLE were not at higher risk. Of note, age, gender and comorbidities (reflected by 'non-rheumatic' treatments) did not have major influence.

In addition to the important epidemiological information provided by Bozzalla Cassione *et al*,[1] we underlined that a high suspicion of COVID-19 infection was not uncommon in our cohort, but with absence of severity. Hydroxychloroquine was ineffective in prevention. There was no correlation with immunosuppressive drugs except for glucocorticoid dose. Disease characteristics were not associated with COVID-19, while comorbidities' influence seemed limited.

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