The impact of SARS-CoV-2 coronavirus infection in patients with systemic lupus erythematosus from a single center in Catalonia

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Abstract

Objective To evaluate the incidence and characteristics of SARS-CoV-2 infection among patients with systemic lupus erythematosus (SLE) and to compare it to that described in the general population.

Methods For 5 weeks, we carried out a cross-sectional study consisting of telephone interviews of SLE patients. We collected epidemiological data, symptoms suggesting COVID-19, results of nasopharyngeal swabs, and ongoing treatments. In those patients who required hospital admission, clinical, radiological, and laboratory features, and outcome were investigated.

Results Four hundred patients with SLE completed the survey. Overall, 4 (1.00%, 95%CI 0.02–1.98) patients were classified as confirmed cases of COVID-19 and 26 (6.51%, 95%CI 4.08–8.94) as possible clinical cases. The incidence of confirmed cases in our series was similar to that of the Catalan population (1.00% versus 0.63%; \(p = 0.456\)), whereas the incidence of possible cases was higher in our series (6.51% versus 1.29%; \(p < 0.005\)). The only difference between SLE patients with confirmed and possible COVID-19 and those without was the percentage of patients who have had contact with a confirmed or possible case of COVID-19 (26.7% versus 9.2%; \(p = 0.003\)).

Conclusions The incidence of COVID-19 in SLE patients with inactive disease is low and, in our series, all cases with confirmed infection recovered.

Key Points

- In a cohort of SLE patients with stable and clinical inactive disease, the incidence of COVID-19 is low.
- All SLE patients with confirmed SARS-CoV-2 infection recovered.

Keywords COVID-19 • Hydroxychloroquine • Outbreak • SARS-CoV-2 infection • Systemic lupus erythematosus

Introduction

According to the data from the European Centre for Disease Prevention and Control, since 31 December 2019 and as of week 2021-5, 106,472,660 cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported, including 2,323,103 deaths [1]. Infections are recognized as major causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [2]. At the start of pandemic, some evidences from in vitro studies suggested that hydroxychloroquine (HCQ), one of the cornerstones of SLE treatment, might play a potential role against SARS-CoV-2 [3]. However, several trials recently published have demonstrated the lack of efficacy of HCQ as both pre-exposure and post-exposure prophylaxis against SARS-CoV2 infection [4, 5].
Latest data from COVID-19 Global Rheumatology Alliance registry including 5790 patients, 1035 (17.9%) were diagnosed with SLE [6].

The aim of the present study was to evaluate the incidence of COVID-19 among SLE patients followed at the Department of Autoimmune Diseases of Hospital Clinic of Barcelona, to compare it to that described in the general Catalan population, and to describe the main characteristics and outcome of severe cases.

Methods

Since 8 April to 12 May 2020, we carried out a cross-sectional study consisting of telephone interviews of SLE patients with outpatient clinic visits made in the previous 6 months or planned follow-up visits in April or May 2020. Patients were identified from the database of the Department of Autoimmune Diseases Department of Hospital Clinic of Barcelona, a Catalan tertiary university hospital. Lockdown was implemented by the Spanish government on March 14, 2020, and in order to minimize face-to-face contact, our hospital decided to transform all outpatient clinic visits to telephone consultations. All participants fulfilled the most recent classification criteria for SLE [7]. We investigated the duration and manifestations of SLE, symptoms suggesting COVID-19, epidemiological and contact history data, results of nasopharyngeal swabs if they were performed, and current treatments. In those patients who required hospital admission, clinical features, treatment, and clinical outcome were investigated. In addition, we collected the activity and damage indexes according to the SLE Disease Activity Index 2000 (SLEDAI-2K) [8] and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [9]. Specifically, SDI was the one from the last visit, and given the lockdown, to calculate SLEDAI, we have used the values from previous laboratory tests plus the clinical information obtained at the telephone survey.

Confirmed cases were defined by a positive SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab samples. We considered possible cases when patients reported cough, fever, shortness of breath, or sudden onset of anosmia, ageusia or dysgeusia [10].

The study was approved by the Hospital Clinic Clinical Research Ethics Committee (HCB/2020/0622). Oral informed consent was obtained from all participants. This study was conducted according to the principles of the Declaration of Helsinki.

Statistical analysis

Continuous variables were described by mean (95% confidence interval (CI)). For categorical variables, data is presented by absolute and relative frequencies. The incidence of COVID-19 was expressed as the percentage (95%CI) of cases with COVID-19 confirmed by nasopharyngeal swab or possible following the World Health Organization guidelines [11] on the total number of patients included in the study. The proportion of patients with confirmed and possible COVID-19 in our cohort was compared to that reported for the general population of Catalonia using the Fisher exact test. Data from Catalanian people were extracted from the Conselleria de Salut de la Generalitat de Catalunya [11]. For statistical evaluation, a contingency table test was used (exact Fisher’s test) to identify significant differences or associations among the groups for qualitative variables, and t-test was used for the quantitative ones. Statistical significance was defined as p < 0.05. All statistical analysis was performed with SPSS 22.0 for Windows (SPSS, Chicago, IL, USA).

Results

Overall, 416 patients with SLE were contacted and 400 completed the survey. The main characteristics and treatments are depicted in Table 1. In all patients, immunomodulatory and immunosuppressant treatments were ongoing for more than 6 months before the telephone survey. The majority of our patients (92%) had an SLEDAI score < 6 and an SDI ≤ 2.

Overall, 4 (1.0%) patients were classified as confirmed cases of COVID-19 and 26 (6.5%) as possible clinical cases. Table 2 shows the main characteristics of the 30 SLE patients with confirmed and possible COVID-19. We did not find differences in the incidence of confirmed cases between our series and the Catalan population (1.0% versus 0.6%; p = 0.456), whereas the incidence of possible cases was higher in our series (6.5% versus 1.3%; p < 0.005).

Table 3 shows the main demographic and clinical features, laboratory results, and outcome of the four SLE patients with confirmed COVID-19. Two patients (#1 and #4) had contact with confirmed cases of COVID-19 at work (both patients are nurses). The first 3 patients required hospital admission. None of the 4 patients had clinical manifestations of SLE activity at the time of diagnosis of COVID-19. From the clinical point of view, the most frequent manifestation was fever, present in all patients, followed by cough (75%), and anosmia and dysgeusia (50%), respectively. Two patients presented with radiographic findings of viral pneumonia on admission. The three patients with hospital admission needed oxygen supplementation, and in patients #1 and #3, the maximum required fraction of inspired oxygen (FiO₂) was 0.24. Patient #2
required high-flow nasal cannula oxygen with a partial pressure of arterial oxygen (PaO₂) of 271 mmHg. He required pulses of intravenous methylprednisolone and non-invasive ventilation with admission to intensive care unit (ICU) due to bilateral pneumonia and respiratory insufficiency. This patient had arterial hypertension, obesity, and end-stage renal disease (ESRD) as comorbidities. Patient #3 required a single dose of intravenous tocilizumab due to worsening of inflammatory parameters. Both cases presented with high plasmatic levels of interleukin-6 (case #2: 37.6 pg/mL and case #3: 27 pg/mL; normal <4.4 pg/mL). Baseline immunosuppressive treatment was withdrawn in patients #2 and #3 during the acute phase of infection. All patients successfully recovered after a median period of 16 days (IQR 13.7–18.5 days). Of note, no patients had SLE flares during or after COVID-19.

When we compared the main characteristics between SLE patients with confirmed and possible COVID-19 and those without COVID-19, the only difference was the percentage of patients who had had contact with a confirmed or possible case of COVID-19 (26.7% versus 9.2%; p = 0.003) (Table 4). Of note, we did not find differences in the treatments used

Table 1 Demographic, clinical characteristics, and treatments of 400 patients with SLE

| Characteristics                        | 
|----------------------------------------|
|                                        |
| Sex (female)                           | 372 (93.0) |
| Mean age at the moment of study (years) | 50.7 (49.5–52.1) |
| Duration of SLE (years)                | 19.5 (18.5–20.5) |
| Lupus low disease activity state*      | 352 (88.0) |
| Complete remission†                    | 82 (20.6) |
| SLEDAI                                 | 2.2 (2.0–2.4) |
| SDI                                    | 0.9 (0.8–1.1) |
| Treatments                             |            |
| Hydroxychloroquine                     | 291 (72.9) |
| Mepacrine                              | 9 (2.3) |
| Any antimalarial                       | 296 (74.2) |
| Prednisone                             | 203 (50.9) |
| Mean dose of prednisone (mg/day)       | 2.3 (2.0–2.7) |
| Immunosuppressants                     | 223 (55.9) |
| Mycophenolate                          | 56 (14.0) |
| Azathioprine                           | 35 (8.8) |
| Methotrexate                           | 24 (6.0) |
| Tacrolimus                             | 12 (3.0) |
| Biologics ‡ (rituximab or belimumab)   | 14 (3.5) |
| Belimumab (ongoing)                    | 11 (2.8) |
| Rituximab (in the last 6 months)       | 3 (0.8) |
| Immunosuppressants and biologics       | 14 (3.5) |
| Antiaggregant                          | 105 (26.4) |
| Anticoagulation                        | 62 (15.5) |
| Epidemiological data                   |            |
| Times per week that you left your home during lockdown | 1.9 (1.6–2.2) |
| COVID-19 contact (yes)                 | 42 (10.5) |
| Number of people with whom you live    | 1.8 (1.7–1.9) |

Quantitative variables are expressed as mean (95%CI) and qualitative variables are expressed as number (percentage)

SDI, SLICC damage index; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; 95%CI, 95% confidence interval

* Lupus low disease activity state: SLEDAI-2K ≤ 4, allowing the patient to be on treatment with ≤ 7.5 mg/day of prednisolone and/or well-tolerated standard doses of immunosuppressive drugs

† Complete remission: SLEDAI-2K = 0 in corticosteroid-free and immunosuppressant-free patients; antimalarials were allowed

‡ Including rituximab and belimumab
Table 2 Main characteristics and clinical features of patients with possible or confirmed SARS-COV-19

| Characteristics                              | 90.0 | 47.9 (43.3–52.4) | 14.7 (11.5–17.9) | 2.1 (1.3–2.9) | 0.9 (0.5–1.4) | 22 (73.3) | 19 (63.3) | 18 (60.0) | 13 (43.3) | 13 (43.3) | 11 (36.7) | 4 (13.3) | 1 (3.3) |
|----------------------------------------------|------|------------------|------------------|--------------|---------------|-----------|---------|----------|---------|---------|----------|---------|--------|--------|
| Sex (female)                                 |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Mean age at the moment of study (years)      |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Duration of SLE (years)                      |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| SLEDAI                                       |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| SDI                                          |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Clinical manifestations of COVID-19          |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Cough                                        |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Headache                                     |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Fever                                        |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Dyspnea                                      |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Dysgeusia                                    |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Anosmia                                      |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Diarrhea                                     |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |
| Nausea                                       |      |                  |                  |              |               |           |         |          |         |         |           |         |        |        |

Quantitative variables are expressed as median (95%CI) and qualitative variables are expressed as number (percentage)

SDI, SLICC damage index; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; 95%CI, 95% confidence interval

Considering studies including only patients with SLE, Ramirez GA et al. [15] found an incidence of 0.9% (41 of 4307 patients with SLE) of RT-PCR-confirmed diagnosis of COVID-19, only slightly exceeding the expected prevalence of COVID-19 in the general population. Two Italian studies performed by telephone survey evaluated the incidence of confirmed and possible COVID-19 in SLE patients [16, 17]. In the former, the authors found a frequency of 3.4% of possible COVID-19 [16]. In the second, Bozzalla Cassione et al. [17] have performed a telemedicine project in order to ensuring follow-up of a cohort of 165 SLE patients during the pandemic in two Italian regions, Lombardy and Emilia-Romagna. They found an incidence of 2.5% of confirmed (by nasopharyngeal swab) COVID-19 and 5% of clinical-COVID-19. The incidence of confirmed cases in their SLE cohort was higher than that reported by the Italian government in the same areas (0.76% in Lombardy and 0.47% in Emilia-Romagna). A recent review of the evidence published so far from studies focused in SLE patients seems to suggest that they may not be at an increased risk of contracting COVID-19 [18]. In this regard, it is possible that patients with SLE have followed protection measures more strictly due to fear of contracting the infection and presenting more severe cases [19]. In our study, the only difference between SLE patients with confirmed and possible COVID-19 and those without COVID-19 was the percentage of patients who had had contact with a confirmed or possible case of COVID-19 (26.7% versus 9.2%; p = 0.003) suggesting that the lockdown effect protecting patients from possible exposure to virus seems to play an important role. In fact, two of those patients with confirmed COVID-19 from our series were nurses with demonstrated epidemiological contact of confirmed cases of COVID-19 at work.

Among the four patients with confirmed COVID-19, one of them developed acute respiratory distress syndrome (ARDS) and required non-invasive ventilation with ICU admission. This patient had ESRD on hemodialysis. In a retrospective study of 101 patients with lupus nephritis from Wuhan, China, two (1.2%) were confirmed to have COVID-19. Both had mild infection and did not require supplemental oxygen [20]. A French multicenter group collected 17 cases of SLE patients with confirmed COVID-19 [21]. Fourteen (82%) patients were admitted to hospital care, 7 of them to ICU. Complications in the form of viral pneumonia were detected in 13 (76%) patients, respiratory failure in 11 (65%), ARDS in 5 (29%), and acute renal failure in 3 (18%) patients, with two patients requiring hemodialysis. The overall mortality was 14% [21]. Data from New York University lupus cohort showed that out of the 41 SLE patients with RT-PCR confirmed COVID-19, 24 (59%) required hospitalization. Half (including HCQ) between patients with or without SARS-CoV-2 infection.

Discussion

The incidence of confirmed cases of COVID-19 in SLE patients in Catalonia, a Mediterranean country of 7.5 million inhabitants at Northeast of Spain, was similar to that reported in the general population. The incidence of possible cases was higher in SLE patients although this result should be interpreted with caution. Some of the clinical manifestations associated to COVID-19 are nonspecific and may be due to other causes.

Data from COVID-19 Global Rheumatology Alliance registry including 600 patients from 40 countries showed that 85 (14%) were diagnosed with SLE, of whom 55% were hospitalized [12]. In a recent retrospective observational study performed in five Spanish reference centers and limited to hospitalized cases of RT-PCR confirmed COVID-19, 16 (7%) out of 228 patients with rheumatic diseases had SLE [13]. A meta-analysis found that patients with SLE, Sjogren’s syndrome, and systemic sclerosis, in aggregate, had a higher prevalence of hospitalization when compared with the other disease groups. In addition, glucocorticoids use that was highly prevalent in this group was significantly associated with the risk of COVID-19 [14].
Table 3

| Sex/age | SLE/COVID-19 duration (years) | SLE manifestations | DD (ng/mL) COVID-19 symptoms | Chest X-ray | CRP (mg/dL) | Ferritin (ng/mL) | Lymphocytes (×10⁹/L) | Treatment | Outcome |
|---------|------------------------------|-------------------|-----------------------------|-------------|-------------|-----------------|---------------------|-----------|---------|
| F/41    | 7                            | Arthritis, fever, | CRP 5.2                      | Bilateral pneumonia | Yes         | 179             | 430               | HCQ 200 | Recovery |
|         |                              | rash, muscle pain |                            | Bilateral pneumonia | Yes         | 521             | 180               | AZT, D/C |          |
| M/36    | 5                            | Arthritis, fever, | 5                           | Normal      | Yes         | 5               | 32               |           | Recovery |
|         |                              | rash, muscle pain |                            |             |             |                 |                   |           |         |
| M/53    | 2                            | Arthritis, fever, | 15                          | Fever, asthenia | Yes         | >1000           | 300               | ND        | ND      |
| F/61    | 10                           | Arthritis, fever, | 0.01                         | Fever, asthenia | Yes         | ND              | ND                | ND        | ND      |

Laboratory features refer the worst COVID-19, coronavirus disease 2019; CRP, C-reactive protein (mg/dL); DD, d-dimer; ESRD, end-stage renal disease; F, female; HCQ, hydroxychloroquine; MPA, mycophenolic acid; MTX, methotrexate; PDN, prednisone; SDI, SLE damage index; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; TCZ, tocilizumab; TZC, teclidizumab. Numbers refer to the dose in mg/day except for MTX which refer to mg/week. Laboratory features refer the worst.

In our study, the use of HCQ of patients with possible or confirmed COVID-19 was similar to that of those patients without infection (73.3% versus 72.2%, p = NS). Moreover, the median dose of HCQ was similar in both groups. It is possible that a population with more severe disease may have a more severe outcome. However, more than half of the analyzed patients were treated with immunosuppressant agents. Second, given the lockdown and the lack of updated laboratory values, to calculate SLEDAI, we have used the values from previous laboratory tests plus the clinical information obtained at the telephone survey. Third, the higher incidence of possible cases in SLE patients should be interpreted with caution. Some of the clinical manifestations associated to COVID-19 are nonspecific and may be due to other causes. Fourth, the majority of telephone surveys were filled by three final year students of the Faculty of Medicine and Health Sciences of University of Barcelona. However, before the present study, they were included in the medical teams in charge of COVID-19 patient care after receiving the corresponding training. Therefore, they were able to recognize the clinical manifestations associated to this viral infection and in case of doubt, senior authors (GE, SPG) discussed case by case. Fifth, due to limited availability of tests for antibodies to SARS-CoV-2 in our setting, true incidence of COVID-19 is unknown, mainly to confirm the possible clinical cases and to identify asymptomatic patients. In addition, SARS-CoV-2 RT-PCR in nasopharyngeal swab samples were performed in only 12 out of 400 (0.03%) SLE patients, including the 4 confirmed cases of COVID-19. The deficits in COVID19 testing in the beginning of the pandemic may skew the confirmed cases towards sicker patients as the ones with milder symptoms/asymptomatic infection were less likely to seek medical care. Finally, telephone surveys were performed during 5 weeks with different date completions. Cases of patients already interviewed could have been lost if the symptoms appeared after the date of survey completion. However, at the time of survey, patients were asked to contact
the investigators if they developed suggestive symptoms of COVID-19 during the following weeks.

In the light of the results of the present study, the incidence of COVID-19 in SLE patients with stable and clinical inactive disease is low and, in our cohort, all cases with confirmed infection recovered.

**Declarations**

**Disclosures**  None.

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