

COVID-19 and mortality in patients with systemic lupus erythematosus

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Abstract

In december 2019, a new disease erupted in Wuhan, China, caused by coronavirus 2019 (COVID-19), which produces severe acute respiratory syndrome (SARS-CoV-2).

Some cases associate COVID-19 with autoimmune disorders; the role of this virus in autoimmunity is poorly understood. Systemic lupus erythematosus (SLE) is an autoimmune disorder. Baricitinib is a Janus kinase inhibitor (JAK) approved for the treatment of autoimmune and inflammatory disorders, recently used for treating severe COVID-19 disease.

We discuss four cases of SLE with COVID-19, two of whom were admitted to the intensive care unit and died, with a history of lupus nephritis; the following two cases survived. The risk factors which increase mortality in SLE are not yet known; however, lupus nephritis was associated with COVID-19 mortality. More studies are needed to understand the risk between autoimmune disorders and COVID-19. (*Acta Med Colomb* 2022; 47. DOI: <https://doi.org/10.36104/amc.2022.2551>).

Keywords: SARS-CoV-2, SLE, baricitinib, mortality, steroids.

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Introduction

Beginning in December 2019, a new disease caused by coronavirus 2019 (COVID-19) broke out in Wuhan, China. It was officially declared a pandemic by the World Health Organization (WHO) in March 2020. It is caused by a strain associated with severe acute respiratory syndrome (SARS) and was named severe acute respiratory syndrome coronavirus type 2 infection (SARS-CoV-2) (1).

A few case reports associating coronavirus and autoimmune disorders have been published, but the role of this virus in autoimmunity is poorly elucidated (2, 3).

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by loss of tolerance of antinuclear antigens and the production of pathogenic autoantibodies. It is a complex disease and may affect various body organs: the skin, eyes, kidneys, heart, muscles and joints. Some viruses involved in its etiology are Epstein-Barr virus (EBV), cytomegalovirus, parvovirus B-19 and retroviruses, which may be possible triggers.

Immune reactions against viral antigens can turn against self-antigens, leading to autoimmunity (molecular mimicry) (4).

Patients with SLE are a unique population for COVID-19 risk. It could be speculated that inherently elevated type I interferon, a characteristic of most patients with SLE, confers a protective effect as a front-line antiviral defense (5).

Baricitinib is a Janus kinase (JAK) inhibitor approved for treating certain autoimmune and inflammatory disorders

which has recently been used for treating severe COVID-19 disease (6).

Rheumatoid arthritis (RA) was the first disease to benefit from the anti-inflammatory properties of baricitinib. It is an adenosine triphosphate competitive kinase inhibitor which selectively, strongly and reversibly inhibits the JAK1 and JAK2 enzymes (6).

Baricitinib prevents viral endocytosis and reduces assembly by inhibiting adaptor protein 2 (AP2)-associated protein kinase 1 and cyclin G-associated kinase in alveolar type 2 cells. It exerts beneficial effects, decreasing the exaggerated inflammatory response (6).

Case descriptions

Case 1

This was a 43-year-old female who had been immunized against COVID-19 with the CanSino vaccine in May 2021. She had a 10-year history of systemic hypertension (HTN) treated with losartan 50 mg/day and metoprolol 100 mg/day. She had had SLE since age 20 and was treated with chloroquine and prednisone up to 2008. In 2010 she had a kidney biopsy reporting class III lupus nephritis, and she received cyclophosphamide pulses until 2012. In 2018 she began rituximab with two applications, and two applications in 2019. During this period, she developed pyoderma gangrenosum which resolved with medication. At the time of admission, she was on mycophenolate 2.5 g/day, chloroquine 150 mg/day, and prednisone 5 mg/day, with monthly follow

up by rheumatology. She was being followed by nephrology every two months, with 15,000 units of erythropoietin applied weekly. Her lupus nephritis was currently classified as stage IV.

On August 5, 2021, she developed a 4/10 intensity headache, Bristol 7 diarrhea for three days, three episodes of vomiting, 38.5° fever after 48 hours, and 94% pulse oximetry saturation (SpO₂) on room air. A polymerase chain reaction (PCR) test for COVID-19 was performed, which was positive, and she was hospitalized due to her history of SLE and fever. She subsequently experienced dyspnea, fever, and tachycardia and was admitted to the intensive care unit (ICU), with no response to non-invasive ventilation. She was therefore treated with advanced airway management, sedation-analgesia and neuromuscular relaxation. Her SpO₂ was 88%, with a fraction of inspired oxygen (FiO₂) of 100% in the prone position and using alveolar protection measures. She developed hypotension, treated with norepinephrine and vasopressin, as well as anuria, and was started on slow continuous renal replacement therapy due to metabolic acidosis and anuria; this type of renal therapy was chosen due to her instability. She had respiratory instability, reaching a partial pressure of arterial oxygen/fraction of inspired oxygen (PaO₂/FiO₂) of 80, with hypotension; she was given enoxaparin 20 mg subcutaneously (SQ) initially due to thrombocytopenia at 45,000. No bleeding was reported; a culture was taken due to the fever, adding a carbapenem and linezolid, and she continued on dexamethasone 8 mg/day for SARS-CoV-2 treatment, with no improvement. Subsequently, the slow continuous therapy was changed to conventional therapy due to slight improvement and the prone position was discontinued, reaching a PaO₂/FiO₂ of 180, on enoxaparin 40 mg/24 hours, with platelets at 130,000. However, she developed sudden onset tachycardia, refractory hypotension, SpO₂ 80%, and D-dimer 20,177 ng/mL, as well as asystole. Cardiopulmonary resuscitation was begun but she did not return to spontaneous circulation, and she was pronounced dead.

Case 2

This was a 55-year-old female diagnosed with SLE 20 years prior, being treated with prednisone 10 mg/day, with class II obesity (34 kg/m² body mass index [BMI]) and hypothyroidism. She began to experience respiratory distress eight days after contagion, with an 80% SpO₂, 2.1 IROX index, RR 34, tachycardia at 130 beats per minute (bpm), fever of 38.5°, positive SARS-CoV-2 PCR, and a CO-RADS 5 chest tomography. She was admitted to the ICU with orotracheal intubation, prone position, mechanical ventilation and 4 mg baricitinib initially and then 2 mg by orogastric tube for three more days. She continued on 40 mg of methylprednisolone per day and was subsequently switched to 20 mg of prednisone. The orotracheal tube culture reported colistin-sensitive *Acinetobacter baumannii* and ESBL (+) klebsiella, and she began treatment. A tra-

cheostomy was performed due to prolonged mechanical ventilation. After an antibiotic dose she developed acute tubular necrosis with kidney failure as a complication, renal and pulmonary dysfunction and death.

Case 3

This was a 62-year-old female with a history of RA diagnosed in 2012, being treated with baricitinib 4 mg/24 h since 2018. She was diagnosed with SLE in 2008 and was treated with prednisone 10 mg/24 h. Her latest exacerbation (skin and joints) was in 2017. On February 15, 2021, she began to experience asthenia, adynamia, a 38.3° fever, dysgeusia, anosmia, abdominal pain and three loose stools. She denied respiratory difficulty, had an SpO₂ of 96%, and a positive SARS-CoV-2 PCR. She began treatment at home, as she refused to go to the hospital, receiving a single 8 mg dose of baricitinib, and then continued with baricitinib 4 mg/day, prednisone 10 mg/24 h, paracetamol 750 mg/8 h, enoxaparin 40 mg/24 h SQ, and hyoscine 1 tablet/8 h until the abdominal pain resolved. A computed axial tomography (CAT) reported CO-RADS 5; she had no respiratory difficulty, received outpatient treatment and improved. On day 14, rheumatology decreased the dose of baricitinib due to abdominal distension and flatus, and she is currently in physical rehabilitation.

Case 4

This was a 50-year-old female with a history of SLE diagnosed in 2005, treated with prednisone 10 mg/24 h since 2007. Her latest exacerbation (joints) was in 2015, and she was treated with azathioprine and nonsteroidal anti-inflammatory drugs (NSAIDs).

On May 20, 2021, she began to experience asthenia, adynamia, a fever of 38.5°, dysgeusia, anosmia, and abdominal pain. She denied respiratory difficulty, with an SpO₂ of 91% and a positive SARS-CoV-2 PCR. She presented to the hospital due to fever, with a simple chest CAT reported as CO-RADS 5. She was admitted to the floor and after 48 h (day 10 of contagion) had an SpO₂ of 84%. She was placed in an awake prone position, with a high-flow nasal cannula. She had an IROX of 5.4, was responsive, and continued in this position for 72 hours, with an SpO₂ of 96%, the flow was decreased to 60 liters, and she was then changed to a reservoir bag mask. On day 16 of contagion, she was changed to the decubitus position, with an SpO₂ of 96%. Inpatient treatment consisted of enoxaparin 60 mg SQ per day, paracetamol 1 gr/8 h, baricitinib with an initial dose of 8 mg/po and 4 mg for 15 days (day 19 of contagion). She was changed to oxygen by nasal cannula at 2.5 L, with 92-94% saturation, cultures were negative, and she was discharged to home on two liters of oxygen by nasal cannula, 10 mg of prednisone and physical rehabilitation.

Tables 1 and 2 show the patients' characteristics. The CARE guidelines for case reports were followed.

Table 1. Demographic characteristics of the population.

	Case 1	Case 2	Case 3	Case 4	n=4
Age, median (IQR)	49	55	62	50	54 (49-62)
Sex, n %	F	F	F	F	
Female					4 (100%)
BMI, median (IQR)	26,4	34	21,2	27,4	27.2 (21.2-34)
Weight, median (IQR)	66	86	49	71	68 (49-86)
Height, median (IQR)	1,58	1,59	1,52	1,61	1.57 (1.52-1.61)
Days of disease course, median (IQR)	18	8	14	8	12 (21.2-34)
Length of stay (days), median (IQR)	18	28	0	14	15 (1-28)
Enoxaparin, median (IQR)	20	60	40	60	45 (20-60)
Mechanical ventilation, n %	Yes	Yes	No	No	2 (50)
CO-RADS, n %	5	5	5	5	5 (100%)
SOFA	11	9	0	2	5.50 (2-11)
APACHE II	29	29	0	8	16.5 (8-29)
COVID 19 vaccine, n (%)	Yes (CanSino)	Yes (CanSino)	No	No	
Yes					2 (50%)
No					2 (50%)
Stay in, n (%)					
ICU	1 (25)	1 (25)			2 (50%)
Hospital floor			1 (25)		1 (25%)
Home (ambulatory)				1 (25)	1 (25%)
MORTALITY, n (%)					
ICU	1 (25)	1 (25)			2 (50%)
Hospital floor					
Home (ambulatory)					

Abbreviations: IQR (Interquartile range), BMI (body mass index), ICU (intensive care unit), SOFA (Sequential Organ Failure Assessment). APACHE II (Acute Physiology and Chronic Health disease Classification System II).

Discussion

We have presented four cases of women with an SLE diagnosis coupled with COVID-19, two of whom developed SARS-CoV-2, were admitted to the ICU and died. In contrast, one patient was treated as an outpatient and another as an inpatient, and both survived. More studies are needed to understand the differential risk between rheumatic diseases and the individual risk associated with the use of various classes of disease-modifying antirheumatic drugs (DMARDs), as well as the long-term effects of COVID-19 in this population (7).

Venous thrombotic episodes have been reported in up to 31% of patients who are critically ill with COVID-19 (8).

In our report, the first case had D-dimer levels > 20,000 ng/mL despite enoxaparin, and she had a fatal outcome. Therefore, we agree that up to 31% of critically ill patients with SLE have venous thrombotic episodes (8). Two of the 24 patients with SLE and COVID-19 (8.3%) needed to be hospitalized and were subsequently diagnosed with micro and macrothrombotic events, emphasizing the need to have a high index of suspicion for this complication, especially in the context of autoimmune rheumatic diseases, including SLE. Also, the mortality rate in patients with SLE and CO-

VID-19 ARDS reached 100% (8); therefore, stricter monitoring must be provided to patients with SLE and SARS-CoV-2 in the ICU, aimed at achieving anticoagulation goals.

Some factors associated with a higher probability of SLE or AR patients being hospitalized for COVID-19 have been identified, including advanced age and the presence of comorbidities, with the most significant one being the dose of prednisone (≥ 10 mg/day) OR 2.05 (95% CI 1.06-3.96) $p=0.03$. No association was found between the use of NSAIDs or antimalarial drugs and hospitalization for COVID-19 (9).

However, the contribution of these cases is that they coincide with Rajalingham et al., who found that lupus nephritis was the only predictive factor of severe or critical SLE COVID-19 (10). We concur with this, since the first case died with a history of lupus nephritis, coinciding as a risk factor for ICU mortality (10).

Patients with autoimmune diseases are vulnerable to infections due to their abnormal immunity and are also susceptible due to the previously used treatments.

This series of cases does not allow conclusions to be drawn regarding the incidence and severity of COVID-19 in SLE, as the number of cases is a limiting factor. However,

Table 2. Biochemical characteristics.

	Case 1	Case 2	Case 3	Case 4	n=4
Leukocytes, median (IQR)	6.7	11.4	10.8	12.5	10.3 (6.7-12.5)
Procalcitonin	1.91	1.4	1	0.9	1.30 (0.90-1.91)
CRP	55.1	76	40	61	58 (40-76)
Creatinine, median (IQR)	2.71	1.04	0.6	1	1.33 (.60-2.71)
Hgb	8.6	10.6	13.2	12.9	11.3 (8.6-13.2)
Plateletes	116,000	180,000	214,000	190,000	17,500 (116,000-214,000)
Neutrophils, median (IQR)	6.1	10.1	8	10	2,000 (6.1-8.0)
Lymphocytes	300	500	600	950	587 (300-950)
D-dimer	20,177	3,400	470	680	1,142.5 (450-21.20)
Ferritin, median (IQR)	215	890	78	430	403 (78-890)
ESR	69	70	28	34	50.25 (20-78)
Baricitinib, median (IQR)	0	4	8	8	5 (2-8)
Steroids, median (IQR)					24 (5-65)
Methylprednisolone		60			
Dexamethasone	8				
Prednisone			20	10	
Prednisone, median (IQR)	5	10	20	10	10 (5-20)
On admission (tx)					

Abbreviations: IQR (interquartile range), tx (treatment), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), Hgb (hemoglobin).

it provides the course of this infection in patients with SLE treated with baricitinib and paves the way for an observational study to identify risk factors associated with severe COVID-19, with comorbidities like chronic kidney disease and obesity.

In this series of cases, the patients with comorbidities were hospitalized and had a worse outcome. The above cases are an example of affected immunity. For now, they are complex therapeutic targets with a broad field for future research, coupling the high lethality of critically ill patients with preexistent comorbidities.

Conflicts of interest

This study received no specific aid from public, commercial or nonprofit agencies. The authors declare no conflicts of interest.

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