Lower Rate of COVID-19 in Lupus Patients Receiving Immunosuppressive Drug Regimens

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Research Article

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Abstract

Introduction Recently, due to the COVID-19 pandemic much concern has been raised about chronic diseases, which could possibly make patients more susceptible, and vulnerable to COVID-19. One of them, is Systemic Lupus Erythematosus(SLE).

Objective This study has tried to find the prevalence of COVID-19 in SLE patients in Golestan province of Iran, and to characterize the clinical course of COVID-19 in these patients. This study has also sought to find possible correlation between the incidence of COVID-19, its clinical manifestations and the medication taken by SLE patients.

Methods We investigated patients who had been enrolled in our rheumatologic diseases registry system. Patients responded to a questionnaire which contained questions about their primary disease, comorbidities, medications, development of new symptoms, and medical services which they received, pertinent to COVID-19, during the period of COVID-19 outbreak. The data were analyzed using SPSS 16 software.

Results This investigation found 25 (7%) COVID-19 positive patients out of the 355 responders. 8 (40%) of them were hospitalized, out of which 2 (8%) required intensive care and later expired. COVID-19 incidence was significantly lower in the immunosuppressed group (2.2% vs 10% P-value 0.005). We didn't find a significant correlation between hydroxychloroquine consumption, and the incidence of COVID-19 in SLE patients. Fever, fatigue, dyspnea, and dry cough were the most common clinical symptoms.

Conclusion Our research has shown that COVID-19 prevalence was lower in immunosuppressed patients. However, broader studies should be conducted to clarify the role of immunosuppression in the development of COVID-19. More research is required.

Key Points

- The results of this study show a lower incidence of COVID-19 in immunosuppressed patients, which is opposed to previous hypotheses about the incidence of infections in patients with SLE. This illustrates the necessity for broader research in this area.
- No significant correlation has been found between the consumption of hydroxychloroquine and the course of COVID-19.
- Our findings suggest that rheumatologists maintain their patients' ongoing treatment since the immunosuppressed state has not been found to be a predisposing factor for COVID-19.
- This study suggests clinicians consider fever, fatigue, dry cough and dyspnea as the most common symptoms in SLE patients.

Introduction

As COVID-19 became a pandemic, much concern was raised about patients with rheumatic diseases. One of which, is Systemic Lupus Erythematosus (SLE). Patients with SLE are more susceptible to developing infections, and may demonstrate more severe forms, compared to the normal population. Some of these patients are also on immunosuppressant drugs, which predispose them to developing infections.[1] One of the most common causes of death in these patients is infection.[2] In addition, there is research that claims hydroxychloroquine(HCQ) which is a common medication for SLE, shows efficacy in the treatment of COVID-19.[3]

The immune system plays a major role in the development of COVID-19. The innate immune reaction to pulmonary tissue damage caused by the virus can lead to acute respiratory distress syndrome (ARDS), which could be the cause of death in these patients[4] So it may be that immune system weakness in immunosuppressed patients brings with it some advantage, with regards to COVID-19.

This study has tried to investigate the clinical course of COVID-19 in patients with SLE, and to evaluate the effect of HCQ on the development of COVID-19 in these patients. Besides these objectives, we have tried to investigate possible correlation between immunosuppression status and COVID-19 among our patients, as well.

Methods

This study investigated the population of patients with a diagnosis of SLE, based on either ACR-1997, or EULAR-2019 criteria, whom had been registered in the database of Golestan Rheumatology Research Center, in Golestan province of Iran. A designed questionnaire consisting of patients' demographic variables, their disease status, medications and new clinical symptoms, was used to classify patients according to WHO COVID-19 case definitions.[5] Patients were asked during phone calls about their experience of COVID-19 symptoms, laboratory tests and clinical imagings related to COVID-19, and any hospitalizations related to this infection.

We collected their information, and divided them into 3 groups, as defined by WHO. Due to social distancing protocols, consideration of SLE patients' health status, and to prevent the spread of COVID-19, we were unable to visit the patients in person, and therefore, there was no opportunity to perform laboratory tests to measure SLE activity in these patients. So we considered disease status as active if they met one of the criteria below:

1. Presence of clinical symptoms, related to SLE, within 2 weeks, confirmed by the patient's rheumatologist.
2. Recent admission to hospital due to major organ involvement related to SLE.
3. Patients who take corticosteroids more than 15mg per day.
4. Patients who are on cyclophosphamide therapy.
5. Patients who take mycophenolate mofetil more than 1500mg per day.

We considered those on Azathioprine, mycophenolate mofetil or methotrexate (more than 12.5 mg/w) , as immunosuppressed patients.

All the participants have given their informed consent to participate in this study.

This study was approved by the Ethics committee of Golestan University of Medical Science.

ID IR.GOUMS.REC.1399.034

2.1 Statistical analysis

Data were analyzed using SPSS 16 software. Chi square test was performed to assess the correlation between COVID-19, and other variables. P-value of less than 0.05 was considered significant.

Results

We contacted 500 SLE patients registered in Golestan Rheumatology Research Center. The mean age of all 500 patients was 40.8 (± 11.9) years, 458 (91.6%) of whom were women. We successfully interacted with 355 patients (71%), and collected the relevant information. The mean age of the responders was 40.1 (± 11.5) years, 326(91.8%) of whom were female. Table-1 shows demographics, disease status, comorbidities, medications, and organ involvements in our patients.

Based on WHO case definitions, we found 25 (7%) patients whom could be enrolled in the COVID-19 positive group.[5] Among them, 11 (44%) were suspected cases, 11 (44%) were probable cases, and 3 (12%) were confirmed cases. The mean age in the COVID-19 group was 43.4 (± 13.2), and 23 (92%) of whom were female. Figure-1 demonstrates the frequency distribution of clinical symptoms related to COVID-19. Fever (68%), fatigue (68%), dyspnea (68%) and dry cough (64%) were the most common symptoms among our patients. Of the 25 COVID-19 positive group members, 8 (32%) patients needed hospitalization, and 2 of them were admitted to ICU who later expired. One of the two patients was a 63-year-old man with a 2-year duration of lupus. He had a history of respiratory disease, and was on mycophenolate mofetil (1.5g/d), prednisolone (15mg/d), HCQ (400mg/d), and methotrexate (10mg/w). He also had pulmonary organ involvement related to lupus. The other expired case was a 63-year-old woman with a 3-year history of lupus. She was on prednisolone (10mg/d) and methotrexate (5mg/d). All 23 other patients recovered. Table-2 shows the characteristics of the patients within the COVID-19 positive, and the COVID-19 negative groups. The mean age of the COVID-19 positive group was higher than the COVID-19 negative group, but it wasn't statistically significant. COVID-19 was significantly more prevalent among patients with respiratory comorbidities than in patients who didn't have these comorbidities (29.4% VS 5.9% P-value<0.001). We also didn't find any correlation between major organ involvement, and COVID-19 infection. There weren't any significant differences between disease activity and developing COVID-19. We also didn't find any correlation between HCQ and COVID-19 incidence in this study. To control for the influence of the dosage rate, we divided the patients' HCQ dosages into two

groups of high dosage ($400\text{mg} \leq$), and low dosage ($<400\text{mg}$). Although COVID-19 was less prevalent among patients on high doses of HCQ, the difference wasn't statistically significant (4.8% VS 6.7% P-value 0.55). The incidence of COVID-19 was significantly higher in non-immunosuppressed patients (10% VS 2.2% P-value 0.005).

Discussion

This study was a survey among SLE patients in Iran, evaluating COVID-19 incidence. The incidence of COVID-19 was 7% in our study, similar to the Cassion et al. study, and less than the Favalli et al. study (12.9%), both from Italy.[6][7] We didn't find a comparable study for the comparison of the rate of hospitalization. Mathian et al. reported an 82 % (14) hospitalization rate among 17 patients, which was higher than our study, (32%),[8] which could be explained by the different admission protocols. The rate of ICU admission was similar to the Cassione et al. study (8% VS 8.3%). We also reported 2 (8%) deaths in our COVID-19 positive group. This number was 2 (11%) in the Mathian et al study. In this study, similar to others, we couldn't find any evidence for the supposed protective effect of HCQ.

In our study, immunosuppressed patients were less susceptible to COVID-19, or more were asymptomatic than non-immunosuppressed patients. This result is compatible with the two previous major outbreaks of Corona virus, in which immunosuppression status was not considered to be a risk factor for more severe forms of SARS or MERS.[9] It is noteworthy that due to their immunosuppressed states, most patients self-isolated, maintained social distancing, and personally followed strict rules regarding COVID-19. This point could act as a confounding factor for our results. More biochemical studies, such as measuring cytokine levels in these patients, and comparing it with other patient groups could help us explain the cause of these findings. The Innate immune response to pulmonary damage caused by SARS-COV2, can lead to acute respiratory distress syndrome, and could be the cause of respiratory failure and death in these patients. Cytokine storm seems to play a major role in severe COVID-19 patients and hence, blocking IL-6, IL-1, and TNF might be beneficial in severe cases.[4] Therefore, the immunosuppressed state might be beneficial, and a point of advantage in SLE patients. This study illustrates the necessity for more research to investigate the role of immunosuppression in the development and progression of COVID-19.

Conclusion

In conclusion, similar to the Favalli study, we recommend rheumatologists to continue patients' ongoing treatment, because immunosuppression could be a protective factor for this outbreak by itself, in addition to the prevention of the flare-ups of the primary disease.

Declarations

Funding info No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Ethics approval This study was approved by the Ethics committee of Golestan University of Medical Sciences ID IR.GOUMS.REC.1399.034 to the effect that all human and animal studies have been approved as appropriate and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate The participants in this study have given informed oral consent to take part in this study. They have had the opportunity to ask, and they have received answers to, any questions they had regarding the study and the use and disclosure of information about themselves for the study.

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Conflict of interest the authors declare no conflicts of interest.

Data availability statement all data relevant to the study are included in the article.

Consent for publication not applicable.

Code availability not applicable.

References

1. Zandman-Goddard G, Shoenfeld Y. SLE and Infections. In: Shoenfeld Y, Rose NR, editors. *Infection and Autoimmunity*. Amsterdam: Elsevier; 2004. p. 491-503.
2. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore)*. 2003;82(5):299-308.
3. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-3.
4. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation*. 2020;27(5):1451-4.
5. "Global Surveillance for COVID-19 Caused by Human Infection ..." Accessed May 23, 2020. https://www.who.int/docs/default-source/coronaviruse/2020-03-20-surveillance.pdf?sfvrsn=e6be6ef1_2.
6. Bozzalla Cassione E, Zanframundo G, Biglia A, Codullo V, Montecucco C, Cavagna L. COVID-19 infection in a northern-Italian cohort of systemic lupus erythematosus assessed by telemedicine. *Annals of the Rheumatic Diseases*. 2020:annrheumdis-2020-217717.
7. Favalli EG, Gerosa M, Murgo A, Caporali R. Are patients with systemic lupus erythematosus at increased risk for COVID-19? *Annals of the Rheumatic Diseases*. 2020:annrheumdis-2020-217787.
8. Mathian A, Mahevas M, Rohmer J, Roumier M, Cohen-Aubart F, Amador-Borrero B, et al. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus

erythematosus under long-term treatment with hydroxychloroquine. *Annals of the Rheumatic Diseases*. 2020;79(6):837-9.

9. D'Antiga L. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl*. 2020.

Tables

Table 1. Demographics, primary disease status, comorbidities, medications, and organ involvements in the population of our patients.	
variables	Responders
Mean age($\pm$ SD) years	40.1($\pm$ 11.5)
Gender	
Female	326(91.8%)
Male	29(8.2%)
Duration of SLE($\pm$ SD) years	8.9($\pm$ 6.3)
Active disease	34(9.6%)
Comorbidities	
Diabetes mellitus	25(7%)
Respiratory diseases	17(4.8%)
Cardiovascular diseases	30(8.5%)
Hypertension	76(21.4%)
Medications	
Prednisolone	273(76.9%)
HCQ ^a	247(69.6%)
Methotrexate	94(26.5%)
Azathioprine	80(22.5%)
Mycophenolate mofetil	42(11.8%)
Organ involvements	
Mucocutaneous	232(65.4%)
Musculoskeletal	305(85.9%)
Renal	118(33.2%)
Hematologic abnormalities	155(43.7%)
Nervous system	104(29.3%)
Pulmonary	51(14.4%)
Eye	101(28.5%)
Cardiac	32(9%)

a.HCQ stands for hydroxychloroquine

Table 2. Characteristics of the patients within COVID-19 positive and COVID-19 negative groups.			
Characteristics	COVID-19 positive (N=25)	COVID-19 negative (N=330)	P-value
Mean age(±SD) years	43.4(±13.2)	39.8(±11.4)	0.13
Women	23(7.1%)	303(92.9%)	0.97
Average duration of SLE(±SD) years	8.2(±6.6)	8.9(±6.2)	0.60
Active disease			
Active	1(2.9%)	33(97.1%)	0.32
Inactive	24(7.5%)	297(92.5%)	
Comorbidities			
Diabetes mellitus+ ^a	2(8%)	23(92%)	0.84
Diabetes mellitus- ^a	23(7%)	307(93%)	
Cardiovascular +	0(0%)	30(100%)	0.11
Cardiovascular -	25(7.7%)	300(92.3%)	
Hypertension +	6(7.9%)	70(92.1%)	0.743
Hypertension -	19(6.8%)	260(93.2%)	
Respiratory disease +	5(29.4%)	12(70.6%)	<0.001
Respiratory disease -	20(5.9%)	318(94.1%)	
Organ involvement			
Muccocutaneus+	15(6.5%)	217(93.5)	0.56
Muccocutaneus-	10(8.1%)	113(91.9%)	
Musculoskeletal+	23(7.5%)	282(92.5%)	0.36
Musculoskeletal-	2(4%)	48(96%)	
Renal +	8(6.8%)	110(93.2%)	0.89
Renal -	17(7.2%)	220(92.8%)	
Hematologic abnormalities +	9(5.8%)	146(94.2%)	0.42
Hematologic abnormalities -	16(8%)	184(92%)	
nervous system +	10(9.6%)	94(90.4%)	0.22
nervous system -	15(6%)	236(94%)	

Eye +	7(6.9%)	94(93.1%)	0.95
Eye -	18(7.1%)	236(92.9%)	
Pulmonary +	5(9.8%)	46(90.2%)	0.40
Pulmonary -	20(6.6%)	284(93.4%)	
Cardiac +	3(9.4%)	29(90.6%)	0.58
Cardiac -	22(6.8%)	301(93.2%)	
Medications			
HCQ + ^b	15(6.1%)	232(93.9%)	0.28
HCQ -	10(9.3%)	98(90.7%)	
Prednisolone +	16(5.9%)	257(94.1%)	0.11
Prednisolone -	9(11%)	73(89%)	
Methotrexate +	10(10.6%)	84(89.4%)	0.11
Methotrexate -	15(5.7%)	246(94.3%)	
Immunosuppressive drugs +	3(2.2%)	133(97.8%)	0.01
immunosuppressive drugs -	22(10%)	197(90%)	
a “+” stands for a positive condition and “-” stands for a negative condition.			
b HCQ stands for hydroxychloroquine.			

Figures

DLOC stands for decreased level of consciousness

Figure 1

Frequency distribution of clinical symptoms in COVID-19 positive group.