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COVID-19 severity and SARS-Cov-2 vaccine safety in pemphigus patients

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Abstract

There are safety concerns in the treatment of pemphigus patients with immunosuppressants, particularly rituximab (RTX), in times of the COVID-19 pandemic. In the beginning, the reports were more pessimistic. However, few reports have recently pointed to manageable courses in this patient group. Therefore, we investigated the disease characteristics and demographic features of pemphigus patients in the period of the COVID-19 pandemic. We aimed to investigate the impact of immunosuppressants on the course of COVID-19 in pemphigus patients. Also, we tried to find out the rate of flares due to COVID-19 and SARS-Cov-2 vaccines. This multicenter study included 247 patients with pemphigus from three tertiary dermatology clinics with the specialized outpatient clinic for autoimmune blistering diseases. Patients were asked standardized questions in person or via telephone calls. Also, demographic data were collected from patients' files. Two hundred forty-four of 247 patients took the survey between August and September 2021. The data of three patients were obtained from the National Health System. We collected the data of all pemphigus patients who visited the clinics at least once in the past 3 years. Among 51 patients having COVID-19, 40 had a non-serious disease, whereas 11 required hospitalization. One patient died because of COVID-19 infection. The number of patients is limited, and data depends mainly on patients' statements. RTX treatment does not require additional safety cautions than other immunosuppressives.

KEYWORDS
COVID-19, pemphigus, rituximab, SARS-CoV-2, vaccine

1 | INTRODUCTION

Pemphigus is a group of IgG-mediated autoimmune diseases in which acantholysis causes flaccid blisters and erosions. It is often treated by systemic corticosteroid and immunosuppressive drugs that may increase the risk of infections and vascular incidents.

The novel β-coronavirus SARS-CoV-2 is the pathogenic agent responsible for COVID-19, a pandemic till March 2020. Many aspects of COVID-19 in the general population are still unclear.[1] Older age,

male sex, and certain comorbidities, including diabetes, obesity, lung, heart, and kidney diseases, were determined as mortality risk factors for COVID-19.[2]

Systemic corticosteroids and immunosuppressive drugs, especially rituximab, are mainstays of pemphigus treatment. Concerns over rituximab treatment are originated from the damage on B-cells which generally takes more than 6 months to recovery. In addition, it requires intravenous administration leading to hospitalization may increase the patient's risk of contact with SARS-CoV-2. Therefore,

early on in the pandemic, Mahmoudi et al. advised postponing rituximab infusions as much as possible.[3]

Limited reports point out that the lately rituximab received pemphigus patients' clinical course of COVID-19 is not severe as feared.[4,5]

Also, a recent meta-analysis reported that patients with autoimmune blistering diseases (AIBDs) with more severe COVID-19 courses had a higher frequency of receiving rituximab treatment.[6] According to this data, the EADV (European Academy of Dermatology and Venereology) AIBD task force still does not recommend using rituximab as maintenance therapy to prevent relapses.[7]

Immunosuppression is identified as an independent risk factor for increased mortality in COVID-19.[8–10] Although the speculations that immunosuppressive treatments may have a potential therapeutic role in the cytokine storm syndrome observed during the SARS-Cov-2 infection course, in reality, the COVID-19 pandemic brings a serious challenge for the management of patients with Pemphigus.[11,12]

Therefore, we aimed to investigate COVID-19 frequency and severity as well as the impact of treatment on COVID course in pemphigus patients. Also, disease flares induced by vaccines and COVID-19 were analyzed.

2 | PATIENTS AND METHODS

The study was conducted between August and September 2021. In this study, three tertiary dermatology clinics with specialized outpatient clinics for autoimmune blistering diseases in Istanbul/Turkey participated. The study was approved by the National Health Minister Ethic committee. Pemphigus vulgaris/foliaceus patients who visited these clinics at least once in the past 3 years were asked standardized questions as a computer-generated survey in person or via telephone calls. Also, demographic data were collected from patients' files. The pemphigus was diagnosed based on the histopathological demonstrating intraepidermal separation with detecting of IgG or/and complement component-3 deposits at the keratinocyte cell membrane via direct immune fluorescence in the skin biopsies and/or the presence of anti-desmoglein 1/3 antibody in serological samples.

Survey aimed to investigate the prevalence and course of COVID-19 and SARS-CoV-2 vaccine status and its effect on disease course in pemphigus patients in Istanbul/Turkey. Disease exacerbation was defined as the occurrence of three or more new lesions within 2 weeks after COVID-19 infection or vaccination or a change in status requiring treatment modification (dose increase or switching to a new treatment). Severity assessment of these patients was made by dermatology specialists who followed them regularly by comparing with their previous clinical conditions since disease severity scores could not be applied regularly under pandemic conditions. Among 247 patients in our databases, 244 took the survey. In addition, the data of three patients who did not visit the clinics or answer the telephone calls during this study; were obtained via National Health System. Patients only with positive real-time polymerase chain reaction for SARS-CoV-2 were defined as COVID-19 diagnosed.

2.1 | Statistical analysis

Data analysis was performed using the IBM SPSS Statistics software (SPSS Inc, Chicago, IL, USA, version 24.0). Descriptive variables are presented as number (percentage) or mean ± SD as appropriate. Pearson's Chi-square test was performed to compare categorical variables. When Pearson's Chi-square test criteria were not met, Fisher's exact test was used. The normality distribution of numerical variables was evaluated using Shapiro–Wilk's test. Finally, Mann–Whitney U and Student's T tests were used to compare independent numerical variables. p values < 0.05 were considered statistically significant.

3 | RESULTS

Table 1 summarizes the main demographics, characteristics, and vaccine status of SARS-Cov-2 infected or non-infected pemphigus patients. Total 51 patients were diagnosed COVID-19, and all patients stated that they were PCR-positive for the virus. Total 11 of 51 (21.57%) patients were hospitalized due to COVID-19. Only one of 11 patients transferred to the intensive care unit and then died. This patient was a 57-year-old male with diabetes mellitus type 2. He had no history of rituximab usage and was not treated by any immunosuppressive treatment for the last 2 years. He was under treatment of 8 mg/day PO methylprednisolone. Table 2 summarizes the characteristics of SARS-Cov-2 infected and vaccinated patients. Ten of 51 (19.6%) patients experienced disease flare after COVID-19, and five of 10 (50%) needed further treatment or treatment change due to pemphigus flare-up. Total 175 of 244 (71.7%) patients were vaccinated against COVID-19. The percentage of vaccine types were 36.9, 34.4, and 0.4 to Sinovac, Pfizer-BioNTech, and Oxford-AstraZeneca, respectively. Total number and percentage of patients who experienced pemphigus flare after vaccination was 18 and 10.3%. Fifteen of 18 experienced flares after the first vaccine administration, and three of 18 after the second administration. Total seven of 18 flares were with Sinovac, and 11 of 18 were with Pfizer-BioNTech. Patients who needed further treatment or treatment change after a vaccination-induced flare was 7 (38.8%). Additionally, one patient other than the study group developed pemphigus vulgaris after the first administration of the Pfizer-BioNTech SARS Cov-2 vaccine during this period.

Non-steroidal adjuvant therapies usage was higher in hospitalized (18.2%) than non-hospitalized (7.5%) COVID-19 diagnosed patients. However, there was no statistical difference in steroid usage and dosage (Table 3).

Table 4 summarizes details of rituximab usage in COVID-19 diagnosed patients. A total of 17 patients were treated by rituximab among SARS Cov-2 infected pemphigus patients. Four of 17 total RTX treated patients were hospitalized due to SARS Cov-2 infection. In subgroup analysis, nine of 17 patients were treated with RTX within 12 months, and three of nine (33.3%) were hospitalized. Only one hospitalized patient was using systemic steroids other than rituximab before COVID-19, whereas the rest were not receiving additional systemic steroid or adjuvant therapy. Therefore, none of them needed to be transferred to the intensive care unit, or none of

TABLE 1 Demographics and characteristics of pemphigus patients

	COVID-19 diagnosed pemphigus patients ($n = 51$), n (%)	Non-COVID-19 pemphigus patients ($n = 193$), n (%)	p value	Hospitalized COVID-19 diagnosed pemphigus patients ($n = 11$), n (%)	Non-Hospitalized COVID-19 diagnosed pemphigus patients ($n = 40$), n (%)	p value
Age, years						
Range	23–83	18–84	0.041[T]	26–83	23–75	0.011[M]
Mean ± SD	48.2 ± 13.3	52.9 ± 14.7		56.9 ± 14.4	45.8 ± 12	
Sex						
Female	22 (43.1)	107 (55.4)	0.117[X]	3 (27.3)	19 (47.5)	0.312[F]
Male	29 (56.9)	86 (44.6)		8 (72.7)	21 (52.5)	
Body mass index, mean ± SD	27.6 ± 7.3	27.3 ± 5,0	0.411[M]	28.5 ± 5.2	27.6 ± 7.7	0.544[M]
Presence of comorbidities	19 (37.3)	85 (44.0)	0.383[X]	7 (63.6)	12 (30)	0.075[F]
Disease duration, years						
Range	1–32	0–30	0.062[M]	1–32	1–26	0.375[M]
Mean ± SD	8.5 ± 7.5	6.7 ± 6.5		10.5 ± 9.2	7.9 ± 7.0	
COVID-19 vaccination status						
Vaccinated	23 (45.1)	152 (78.8)	0.001[X]	3 (21.6)	20 (50)	0.305[F]
Non-vaccinated or unknown	28 (54.9)	41 (21.2)		8 (72.7)	20 (50)	
COVID-19 vaccination type						
Sinovac	9 (17.6)	81 (42)	N/A	1 (9.1)	8 (20)	N/A
Pfizer-BioNTech	14 (16.7)	70 (36.3)		2 (18.2)	12 (30)	
Oxford-AstraZeneca	0 (0)	1 (0.5)		0 (0)	0 (0)	
Non-vaccinated or unknown	28 (40.6)	41 (21.2)		8 (72.7)	20 (50)	

Note: Statistically significant p values are indicated in bold.
[T]Student's T test, [M]Mann Whitney U test, [F]Fisher's Exact test, [X]Chi-square test.
Abbreviations: MP: methylprednisolone, N/A: non-available.

them died due to COVID-19 infection. The mean hospitalization durations were 10 ± 3.9 versus 9.25 ± 3.4 among rituximab treated and total COVID-19 diagnosed patients, respectively. The mean ages of hospitalized total and rituximab treated patients were 56.9 ± 14.4 and 51 ± 13.6, respectively. However, two patients who were recently rituximab treated and hospitalized patients were young (26 and 47 years), and they did not have comorbidities. The percentage of females in total hospitalization patients was 72.7, whereas in rituximab treated patients was 25. All discharged patients' health and general condition were well.

4 | DISCUSSION

Our study investigated the prevalence, course of COVID-19, and flares due to infection and vaccination. Percentage of hospitalization among total, RTX non-treated and RTX treated within 12 months were 21.57%, 23.52%, and 33.3%, respectively. Longer hospitalization duration in rituximab treated patients could be due to more

caution of doctors to these patients. Need to intensive care and death rate was 1/51 (1.96%) and 0/17 (0%) in total and RTX treated SARS-Cov-2 infected pemphigus patients. According to Worldometer charts, by October 4 rate of death due to COVID-19 in the general population of Turkey was 0.9%.[13] We can not compare death rates in the general population and pemphigus patients because they are not age-matched groups, and the number of patients is low in the study group. However, it is important that none of the patients who were treated with RTX needed intensive care or died because of COVID-19.

Our results were similar to newly released data despite more pessimistic early papers. The data of a pemphigus foliaceus patient who was infected by SARS-CoV-2 2 months after RTX infusion were reported. She required hospitalization but did not need intensive care, and she completely recovered.[2] An article from Italy reported that 19.4% of AIBDs patients experienced mild to moderate symptoms, while one PV patient (3.2%) with previous breast cancer required hospitalization but later recovered.[14] Shahidi-Dadras et al. reported five COVID-19 cases with a mild or moderate course in the total 45 RTX

TABLE 2 Characteristics of COVID-19 diagnosed and vaccinated patients

Characteristics	Pemphigus patients with COVID-19 status known ($n = 244$), n (%)	p value
COVID-19, total	51 (20.9)	0.999[F]
Pemphigus vulgaris patients	49 (20.1)	
Pemphigus foliaceus patients	2 (0.8)	
Hospitalization due to COVID-19, total	11 (4.5)	0.999[F]
Pemphigus vulgaris patients	11 (4.5)	
Pemphigus foliaceus patients	0 (0)	
Need for intensive care unit due to COVID-19, total	1 (0.4)	0.999[F]
Pemphigus vulgaris patients	1 (0.4)	
Pemphigus foliaceus patients	0 (0)	
Death due to COVID-19, total	1 (0.4)	0.999[F]
Pemphigus vulgaris patients	1 (0.4)	
Pemphigus foliaceus patients	0 (0)	
Duration of discharge in hospitalized patients, days, mean ± SD	10 ± 3.9	
Patients who experienced disease flare after COVID-19, n/COVID-19 patients	10/51 (19.6)	
Patients who needed further treatment or treatment change after COVID-19, n/patients with disease flare	5/10 (50)	
COVID-19 vaccination rates among patients, total	175 (71.7)	
Sinovac	90 (36.9)	
Pfizer-BioNTech	84 (34.4)	
Oxford-AstraZeneca	1 (0.4)	
Patients who experienced disease flare after COVID-19 vaccination, n/ vaccinated patients	18/175 (10.3)	
Vaccine types in patients who experienced a disease flare		
Sinovac	7/175 (4.4)	0.333[X]
Pfizer-BioNTech	11/175 (6.9)	
Disease flare period according to vaccination dose, n/patients with disease flare		
After the first dose	15/18 (83.3)	**<0.001** [X]
After the second dose	3/18 (16.7)	
Patients who needed further treatment or treatment change after COVID-19 vaccination, n/patients with disease flare	7/18 (38.8)	

Note: Statistically significant *p* values are indicated in bold.
[F]Fisher's Exact test, [X]Chi-square test.

treated pemphigus patients. None of the COVID cases were treated with RTX within 12 months.[15] A study from Turkey reported only one case of mild COVID-19 among 48 pemphigus patients treated with RTX during the last 5 years. The authors stated that the patient received RTX infusion 7 months before COVID-19.[16] Another study by Mahmudi et al. showed that the risk of COVID-19 and hospitalization rate is decreased significantly with each passing month from the last RTX infusion.[17]

According to a recent review, overall AIBDs patients, 0.8% showed severe symptoms requiring hospitalization, and 0.4% died because of COVID-19, mostly being elderly and/or having comorbidities.[6] However, more disappointing results than ours recently reported that 19 cases among autoimmune blistering disease patients from the USA. Three patients who received rituximab before six or more months prior recovered without any treatment. But other two of three, who received rituximab within 5 months, died. It should be

TABLE 3 Treatment modalities in the COVID-19 diagnosed and non-diagnosed patients

Systemic treatment modalities	COVID-19 diagnosed pemphigus patients ($n = 51$), n (%)	Non-COVID-19 pemphigus patients ($n = 193$), n (%)	p value	Hospitalized COVID-19 diagnosed pemphigus patients ($n = 11$), n (%)	Non-Hospitalized COVID-19 diagnosed pemphigus patients ($n = 40$), n (%)	p value
Systemic corticosteroid usage during pandemic						
Yes	22 (43.1)	99 (51.3)	0.300[X]	4 (36.4)	18 (45)	0.737[F]
No	29 (56.9)	94 (48.7)		7 (63.6)	22 (55)	
Daily systemic corticosteroid dosage, n/patients treated with corticosteroids						
<16 mg MP or equivalent	20/22 (90.9)	72/99 (72.7)	0.071[X]	4/4 (100)	16/18 (88.9)	0.999[F]
≥16 mg MP or equivalent	2/22 (9.1)	27/99 (27.3)		0/4 (0)	2/18 (11.1)	
Non-steroid adjuvant therapies usage during the pandemic (Methotrexate, Mycophenolate, Azathioprine, Dapsone)	5 (9.8)	43(22.27)		2 (18.18)	3 (7.5)	0.999[F]
History of IVIG treatment						
Yes	10 (19.6)	16 (8.3)	**0.020[X]**	4 (36.4)	6 (15)	0.114[F]
No	41 (80.4)	177 (91.7)		7 (63.6)	34 (85)	
History of rituximab treatment						
Yes	17 (33.3)	40 (20.7)	0.058[X]	4 (36.4)	13 (32.5)	0.999[F]
No	34 (66.7)	153 (79.3)		7 (63.6)	27 (67.5)	

Note: Statistically significant p values are indicated in bold.
[F]Fisher's Exact test; [X]Chi-square test.
Abbreviations: IVIG, intravenous immunoglobulin; MP, methylprednisolone; N/A, non-available.

TABLE 4 Characteristics of COVID-19 diagnosed patients with a history of rituximab treatment

		Hospitalization	Age-year/comorbidities/ cotreatments in hospitalized patients	Vaccine status before COVID-19	COVID-19 treatment/ duration of hospitalization
SARS-Cov-2 PCR (+) in RTX treated patients (n)	17	4/17			
Within 15 days (n)	1	1/1	47/−/daily 40 mg MP	Non-vaccinated	Standard+IVIG, Convalance plasma/14 days
Between 15 days and 1 month (n)	1	1/1	26/−/−	Non-vaccinated	Standard/8 days
Between 1 and 6 months (n)	1	0			
Between 6 and 9 months	3	0			
Between 9 and 12 months (n)	3	1/3	67/IBH, overweight/−	Non-vaccinated	Standard/5 days
12–15 months (n)	2	1/2	60/Ht, overweight/−	Pfizer/BioNTech (single dose)	Standard/10 days
15–18 months (n)	3	0			
18–24 months (n)	2	0			
24–68 months (n)	1	0			

noted that additional independent risk factors other than rituximab treatment might worsen the outcomes.[18] In July 2021, Kridin et al. reported total 12 (1%) patients infected by SARS-CoV-2 in 1236 patients with pemphigus. Five of 12 (41.7%) patients were hospitalized, but did not need mechanic ventilation. Only one pemphigus patient died following COVID-19. Consistent with our results; they did not find elevated mortality risk in pemphigus patients. In addition, the duration of disease and systemic corticosteroid or immunosuppressive agents usage did not predict severe COVID-19.[19]

The EADV (European Academy of Dermatology and Venereology) AIBD task force currently does not recommend the use of rituximab to prevent relapses, especially for non-vaccinated patients.[6] The EADV started an international registry for AIBD patients with confirmed COVID-19. However, they did not formally report the results yet. The results of this registry certainly will draw a road map in these hard-to-manage groups.

The patient's awareness of the risks inherent in their chronic illness may lead to very cautious patients' lifestyles, and the behaviors of patients could help our relatively relieving results.

We have insufficient data to predict the long-term effects of the SARS-CoV-2 infection, particularly for patients with profound immune system dysfunction such as pemphigus. Therefore, while larger data are needed, the risk should be calculated for each patient.

All available COVID-19 vaccines are either inactivated or mRNA containing vaccines and they are both non-live and safe for immunosuppressed patients. Even though the data on the safety and efficacy of COVID-19 vaccines in immunocompromised patients are scarce, it is recommended to vaccine these vulnerable groups in the light of previous vaccine experiences.[20] There was no specific data in the literature that analyzed disease flare-up after COVID-19 in pemphigus patients. Only one paper recently reported five AIBD patients who experienced disease flare due to COVID-19 vaccination. Two of five those patients were diagnosed with pemphigus vulgaris. One experienced flare with Moderna mRNA-1273 and the other with Pfizer-BioNTech vaccine.[21] Our study revealed that 10 of 51 (19.6%) and 18 of 175 (10.3%) patients experienced disease flare after SARS-Cov-2 infection and SARS-CoV-2 vaccines, respectively. The flares by vaccines are mainly after the first doses. It supports that there is no need to cancel following vaccine doses despite flares. The need for further treatment or treatment change was 50% and 39% in COVID-19 and vaccine groups, respectively. Additionally, one patient other than the study group developed pemphigus vulgaris after the first administration of the Pfizer-BioNTech SARS-CoV-2 vaccine.

Our study has some limitations. Firstly, the number of patients is not high enough. Secondly, data collection depends mainly on patients' statements. Moreover, rituximab treated patients were limited due to hesitations at the pandemic's beginning. Although our study has some limitations, each data of the pemphigus patients treated with RTX under the pandemic condition is very valuable.

In conclusion, it seems that the scenarios in RTX treatment are not scary as is expected. Also, it is important to keep in mind that SARS-CoV-2 infection and vaccines may worsen disease course and may trigger the pemphigus disease. Therefore, it is essential to measure all advantages and disadvantages of treatment choice in these hard to manage patient groups.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: Mehmet Salih Gürel, Züleyha Özgen, Hasan Aksoy, Özlem Akın Çakıcı, Ozan Erdem, Ayşe Esra Koku Aksu, and Asude Kara Polat. *Data collection or processing*: Züleyha Özgen, Hasan Aksoy, Özlem Akın Çakıcı, Mehmet Salih Gürel, Ozan Erdem, Ayşe Esra Koku Aksu, and Asude Kara Polat. *Analysis of interpretation*: Ozan Erdem, Züleyha Özgen, Hasan Aksoy, Mehmet Salih Gürel, and Özlem Akın Çakıcı. *Literature search*: Züleyha Özgen, Mehmet Salih Gürel, Hasan Aksoy, Özlem Akın Çakıcı, Ayşe Esra Koku Aksu, and Asude Kara Polat. *Writing*: Züleyha Özgen, Hasan Aksoy, Özlem Akın Çakıcı, Ozan Erdem, Ayşe Esra Koku Aksu, Asude Kara Polat.

ETHICAL APPROVAL

Local ethics committee approval was obtained with the protocol number of 09.2021.699, dated 04.06.2021.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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