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Can rituximab be used in the treatment of pemphigus vulgaris during the COVID-19 pandemic?

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Abstract

Rituximab is a monoclonal antibody that targets CD20, a B-lymphocyte antigen; that leads to a decline in the B-cell counts for at least a year. The patients who have received rituximab treatment in the previous 5 years with the diagnosis of pemphigus group of diseases at Cerrahpaşa Medical Faculty were questioned for COVID-19 infection. A total of 48 patients were included in this study; only one male patient had COVID-19 infection which had a mild course. There is no significant difference in the total number of lymphocytes between patients who have received rituximab within the previous 5 years or last year. The number of lymphocytes is independent of the number of courses of rituximab treatment received. Therefore, we suggest that all pemphigus patients who have received rituximab treatment within the previous 5 years should be careful of the preventive measures against the COVID-19 infection irrespective of the number of treatment courses or the number of years which has passed since the treatment. The disease course was mild in the only infected patient. Thus, rituximab may be used in the treatment of pemphigus vulgaris during the COVID-19 pandemic if its use is necessary.

KEYWORDS
CD20, COVID-19, lymphocyte, pemphigus, rituximab

1 | INTRODUCTION

Rituximab is a monoclonal antibody that targets CD20, a B-lymphocyte antigen; that leads to a decline in the B-cell counts.[1] It is used in the treatment of both pemphigus vulgaris and pemphigus foliaceus. It may be used in the first-line treatment along with systemic corticosteroids; or it may be added to the corticosteroid treatment in refractory cases.[2] T-lymphocyte subsets (CD4 and CD8) are known to have an impact on disease severity and clinical outcomes in the COVID-19 infection.[3] The B-lymphocyte depleting effect of rituximab is known to last for up to 7 years in patients who have received repeated treatments; however, it has no known effect on T-lymphocytes.[4] With this study, we aim to determine if rituximab treatment increases the risk of COVID-19 infection in pemphigus vulgaris patients; and thereby we aimed to validate its use during the following course of the pandemic.

2 | PATIENT AND METHODS

The patients who have received rituximab treatment between September first, 2015 and September first, 2020 with the diagnosis of pemphigus group of diseases at İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Dermatology Department, Bullous Diseases Outpatient Clinic were included in this study. The patients who have been lost to follow-up, who have died or who were unable to provide accurate answers to our questions were excluded from this study. The use of concomitant therapy was not an exclusion criterion and patients with all types of adjuvant drugs were included in this study. The gender, age, current lymphocyte count of each patient were noted. Each patient was questioned for COVID-19 infection. Any patient with a positive PCR or symptoms/computerized tomography suggestive of the COVID-19 infection were accepted as having had COVID-19 infection in our study. If the patient has had a

COVID-19 infection, he was questioned about the course of the disease.

2.1 | Ethical statement

The approval of the Cerrahpaşa Medical Faculty Ethics Commitee was taken before initiating the study.

2.2 | Statistical analysis

Statistical analysis was done using SPSS 21. Descriptive analysis was analyzed with average, SD, median, and quarantiles (25-75). Continuous variables were analyzed with the Shapiro Wilk test. The relationship between the lymphocyte count and the total number of treatment courses was analyzed with Kruskal-Wallis test. The patients who have received a single treatment course are compared to those who have received multiple courses in terms of lymphocyte count using the Mann-Whitney *U* test. A *P* value below .05 was considered as significant.

3 | RESULTS

A total of 48 patients were included in this study. Fourteen patients (29.2%) were male and 34 patients (%70.8) were female. The mean age of all patients was 45.58 ± 12.1 years. The mean age of male patients was 41.5 ± 11.2 years and the mean age of female patients was 47.2 ± 12.3 years.

Thirty-five patients (72.9%) received a single course of treatment; nine patients (18.8%) received two courses, three patients (6.3%) received three courses and one patient (2.1%) received four courses. Only one patient had been diagnosed with COVID-19 infection; who has received a single treatment course and has a lymphocyte count of $1.2 \times 10^3/\mu l$. The mean lymphocyte count of all patients was 1.92 $\pm 0.81 \times 10^3/\mu l$. There is no significant relationship between the total number of treatment courses received and the lymphocyte count (P = .086). Furthermore, no significant relationship was found between the number of treatment courses received and the lymphocyte counts (P = .084).

Of all the patients, 17 (35.4%) received rituximab treatment within the last year. Two of the patients (4%) were diagnosed as pemphigus foliaceus and 46 (96%) patients had pemphigus vulgaris. The mean lymphocyte count of the patients who has received the treatment within the previous year was $175.8 \pm 0.92 \times 10^3/\mu l$. The mean lymphocyte count of other patients was $2.02 \pm 0.75 \times 10^3/\mu l$. There is no significant difference between the lymphocyte counts of these two groups (P = .206; Table 1).

4 | DISCUSSION

The COVID-19 disease has emerged in China in December 2019; and it soon has evolved into a pandemic.[5] Decreased lymphocyte counts were found to lead to a severe course of COVID-19.[6] Rituximab decreases the B-cell counts and the overall lymphocyte counts. The patients receiving rituximab treatment are more prone to viral infections than the normal population.[1]

Previously, it was reported that rituximab use increased the hospitalization rate, made the prognosis of the disease worse, and increased the mortality rate in patients with a group of rheumatologic diseases. The disease-specific mortality rate in patients receiving rituximab was 37.5%. On the other hand, the mortality rate of the COVID-19 was calculated as 28% in a multicenter study. Thus, rituximab use has the potential of leading to an unfavorable disease course or outcome in patients during the COVID-19 pandemic.[7] Safavi et al[8] studied the effect of the use of B-cell depleting agents in the course of COVID-19 pandemic. Of their 712 patients, only 34 (4.8%) had COVID-19 infection. Only two of these 34 patients required

TABLE 1 Clinical characteristics of the patients

	Patients who received rituximab within the last year (N = 17)	Patients who received rituximab in previous years (N = 31)	Overall (N = 48)
Age (years)*	46.2 ± 12.1	45.1 ± 12.5	45.58 ± 12.1
Sex (%)			
Female	8 (47.1%)	26 (83.9%)	34 (70.8%)
Male	9 (52.9%)	5 (16.1%)	14 (29.2%)
COVID-19 (%)			
Positive	1 (5.9%)	0(0%)	1 (2.1%)
Negative	16 (94.1%)	31 (100%)	47 (97.9%)
Lymphocyte count $10^3/\mu l$	1758.8 ± 919.2	2023.3 ± 748.6	1927.6 ± 814.7
Pemphigus vulgaris (%)	16 (94.1%)	30 (96.8%)	46 (95.8%)
Pemphigus foliaceus (%)	1 (5.9%)	1 (3.2%)	2 (4.2%)

hospitalization and none of the patients were admitted to the intensive care unit. The use of B-cell depleting agents was found to increase the risk of COVID-19 infection 2.6 times. Yet, the disease courses were mild to moderate and the mortality rates did not increase.

The management of pemphigus vulgaris and other autoimmune bullous diseases were challenging during the COVID-19 pandemic. Pemphigus vulgaris is a potentially mortal disease without treatment; the use of immunomodulatory drugs including rituximab had a pivotal role in decreasing the mortality rate of pemphigus vulgaris.[9] Immunomodulatory drugs increase the rate of viral infections and it is important to note that infections could lead to relapses of pemphigus vulgaris.[10] It is known that the combination therapy of short term systemic corticosteroids with Rituximab is more effective and has less adverse effects (including infections) compared to systemic corticosteroids alone in the treatment of pemphigus vulgaris.[11] The addition of Rituximab does not increase the rate of contracting the virus compared to the use of corticosteroids alone. However, the effects of Rituximab is known to last for at least a year. Therefore, COVID-19 virus-specific plasma cells could not be produced by the patients who have received Rituximab treatment within the previous year and a more prolonged or severe course of COVID-19 infection is expected compared to the healthy population.[10] Similarly, a granulomatosis polyangitis patient who has received rituximab treatment was reported by Koff et al[12] for prolonged incubation period and poor humoral response.

Only one of our patients has contracted COVID-19 virus; he was tested PCR-positive. He has received a single course of Rituximab treatment for refractory pemphigus vulgaris 7 months ago; and had a lymphocyte count of $1.2 \times 10^3/\mu l$. He is 38 years old and has no known risk factor for the COVID-19 infection such as diabetes mellitus or hypertension. He was not receiving corticosteroid therapy or any other immunosuppressive agent. He had mild symptoms, did not require hospital or ICU admission and has fully recovered from the disease with 5 days of favipiravir treatment. The B-lymphocyte depleting effect of Rituximab is known to last at least 1 year and up to 7 years.[4,10] Previous literature suggests that Rituximab treatment within the previous year increases the severity and duration of COVID-19 disease.[7,8] However, we have found no significant difference between the lymphocyte counts of patients who have received Rituximab treatment within the previous 5 years compared to those who have received it last year. Our results could be supported more by the use of flow-cytometry, which unfortunately is more expensive and could not be requested for every patient. We suggest that the use of Rituximab within the previous 5 years poses a risk of increased severity and duration of COVID-19 disease. Thus, not only the patients who have received Rituximab last year but also those who have received it within the previous 5 years should pay extra attention in terms of disease prevention. Similarly, Shahidi-Dadras et al[13] reported that out of their 45 pemphigus vulgaris patients who have received rituximab treatment within the previous 4 years only five patients have contracted COVID-19 and none of these patients have received the therapy in the last year. Furthermore, we have found that the lymphocyte count is independent of the number of Rituximab treatment courses received. Therefore, the risk of having a prolonged and severe COVID-19 infection is independent of the number of treatment courses received. Our only patient who has contracted the virus had received a single treatment course within the previous year.

There are three review articles regarding the management of pemphigus vulgaris patients during the COVID-19 pandemic. All of the authors agree that rituximab use should be postponed during the pandemic.[14–16] Since infections can also lead to disease relapses[10] in alignment with our results, we suggest that rituximab therapy could be given during the pandemic if the benefit outweighs the risk, as in our patient's case.

In conclusion, rituximab treatment has the potential of worsening the prognosis of COVID-19 infection. There is no significant difference in the total number of lymphocytes between patients who have received rituximab within the previous 5 years or last year. Furthermore, the number of lymphocytes is independent of the number of courses of rituximab treatment received. Therefore, we suggest that all pemphigus patients who have received rituximab treatment within the previous 5 years should be careful of the preventive measures against the COVID-19 infection irrespective of the number of treatment courses or the number of years which has passed since the treatment. However, COVID-19 had a mild course in our only infected patient. Thus, rituximab may be used in the treatment of pemphigus vulgaris during the COVID-19 pandemic if its use is absolutely necessary.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design of the study: Tugba Kevser Uzuncakmak, Defne Ozkoca; acquisition of data: Tugba Kevser Uzuncakmak, Defne Ozkoca, Ozge Askin; analysis and/or interpretation of data: Tugba Kevser Uzuncakmak, Defne Ozkoca, Ozge Askin, Zekayi Kutlubay.

ETHICS STATEMENT

We conducted our research according to the World Medical Association Declaration of Helsinki and obtained the approval of the local ethics committee.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs

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