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Original Article

Rituximab treatment for refractory and moderate-to-severe pemphigus patients in the pandemic era: A single-center retrospective study

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Abstract

Background: The management of refractory pemphigus in the pandemic conditions is challenging. There are limited data comparing the safety of rituximab and other immunosuppressive therapies during the COVID-19 pandemic. **Objectives:** We evaluated the safety and efficacy of rituximab and conventional treatments in patients with pemphigus who received treatment during the COVID-19 pandemic period. **Methods:** The patients with pemphigus treated with immunosuppressive treatments in a university hospital between September 2020 and May 2023 were retrospectively evaluated. All patients initially received conventional treatments. Fifteen of them who were refractory to prior treatments or could not use prednisolone due to adverse effects received rituximab. Eighteen patients were treated with only conventional treatments. **Results:** Thirty-three patients with a mean age of 50 ± 15 years were included in the study. Twenty-two of the patients (66.7%) were female. The baseline mean pemphigus disease area index (PDAI) score of the patients was 37 ± 34 (range: 4–168). The mean follow-up time was 13.8 ± 6.8 months. The mean PDAI scores were significantly lower after treatment in both rituximab and conventional treatment groups (P: 0.001, $P < 0.001$; respectively). In the rituximab group, the monthly mean prednisolone dose was statistically reduced after rituximab treatment compared to before treatment ($P < 0.001$). There was no statistically significant difference in the relative odds of COVID-19 positivity or death between the groups (3.06 (95% [confidence interval (CI): 0.68–13.79]; 0.57 [95% CI: 0.05–7.00], respectively). Of 11 patients diagnosed with COVID-19, one patient (1/7, 14.3%) in the rituximab group and two patients (2/4, 50%) in the conventional treatment group died from SARS-CoV-2. **Conclusion:** We observed that rituximab treatment was effective and safe for treatment-resistant moderate-to-severe pemphigus patients during the COVID-19 pandemic.

Key words: COVID-19, efficacy, refractory pemphigus, rituximab, safety

Introduction

Pemphigus encompasses a group of rare autoimmune blistering diseases (AIBD) mediated by autoantibodies against desmosomal adhesion proteins of the skin and/or mucosa. This disease is life-threatening if left untreated, and it can be complicated by adverse effects from the long-term use of immunosuppressive treatments such as opportunistic infections, cardiovascular, psychiatric, and bone disorders.[1,2]

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Rituximab is a monoclonal antibody that targets the CD20 antigen on B lymphocytes and is considered as the first-line therapy for moderate-to-severe pemphigus vulgaris in adults.[3] The administration of rituximab results in the suppression of CD20-expressing B lymphocytes, which includes most pre-B cells, mature B lymphocytes, and memory cells, while plasma cells and existing antibody levels are not altered.[4] The recovery of B cell count may take up to 12 months.[2] B cells are known to play a crucial role in protective immunity against SARS-CoV-2 which affects the clinical course of the COVID-19 infection and the vaccine responses.[5] In addition, rituximab has been shown to reduce the humoral immune response, particularly in elderly patients, individuals taking corticosteroids and those with low basal antibody levels.[4] In the early phase of the COVID-19 pandemic, due to its long-lasting effects on the humoral response to infection, many experts recommended that rituximab therapy must be weighed against the risks of conventional immunomodulatory treatments.[6,7] Subsequently, some reports indicated that rituximab use in different disease groups such as rheumatoid arthritis and multiple sclerosis, was associated with worse COVID-19 outcomes.[8,9]

In our clinic, in the early stages of the pandemic, when the COVID-19 vaccination was not available, we postponed the rituximab treatment, and preferred other immunosuppressive agents and/or intravenous immunoglobulin (IVIG) along with systemic corticosteroids as recommended by experts. However, in a subset of patients, it was not possible to taper the steroid dose due to relapses of severe pemphigus disease. In addition, some patients could not use steroid treatment due to steroid-induced avascular necrosis or psychosis. In consideration of these and after the availability of vaccination in our country, rituximab was administered to pemphigus patients who needed further treatment.

The management of refractory pemphigus is extra challenging in the pandemic conditions. There are limited data comparing the safety of rituximab and other immunosuppressive therapies during the COVID-19 pandemic. Therefore, in this study, we aimed to evaluate the safety and efficacy of rituximab and conventional adjuvant treatments in patients with pemphigus during the COVID-19 pandemic period.

Materials and Methods

This single-center retrospective observational study was conducted in a specialized outpatient clinic for AIBD in a university hospital between September 2020 and May 2023. Pemphigus diagnosis was made based on the following criteria: pathological findings of a lesion showing intraepidermal vesicles, suprabasal acantholysis, and positive direct immunofluorescence from perilesional skin demonstrating intercellular deposition of immunoglobulin G and/or C3.

Initially, a total of 52 patients with active pemphigus disease were identified in the given period. Among these, 4 patients who received topical treatments, and two patients with malignancy were excluded from the study. Until the COVID-19 vaccine became available in our country, all patients initially received conventional treatments (systemic corticosteroid ± azathioprine ± IVIG). Thirteen of 46 patients who started systemic treatments were lost to follow-up during the pandemic. A total of 33 patients were included in the study. Fifteen of them who were refractory to prior conventional treatments or could not use prednisolone due to adverse effects received rituximab treatment (±prednisolone, ±IVIG). Patients who fail to respond to conventional treatments are considered to have refractory pemphigus. Rituximab was given at least 4 weeks after the administration of a full course of COVID-19 vaccinations (n: 14; except one 10-year-old patient) and obtaining patient consent. All patients were screened for SARS-CoV-2 infection by polymerase chain reaction (PCR) before rituximab infusion. Rituximab induction therapy was administered in adult patients in 2 doses of 1 g/day with an interval of 15 days, and in 4 doses of 375 mg/m^2 once a week in one pediatric patient. Eighteen patients were treated with only conventional treatments [Figure 1]. The patients in two groups were compared regarding clinical baseline characteristics, monthly prednisolone dosage, pemphigus endpoints, COVID-19 positivity, and course.

The baseline and posttreatment disease severity of the patients were determined by the "pemphigus disease area index" (PDAI) score.[10] Pemphigus patients are classified as mild, moderate, and severe based on PDAI cutoff values (≤8, 9–24, and ≥25, respectively), recommended by Krain *et al*.[11] Complete remission off therapy was defined absence of new or established lesions without any systemic therapy for at least 2 months. Complete remission on therapy was defined absence of new lesions while the patient is receiving minimal therapy. Other pemphigus endpoints including partial remission off therapy, partial remission on minimal therapy, and relapse were evaluated according to consensus statements by Murrell *et al*.[12]

Patients were followed up by the same dermatologist prospectively and data including demographics of the patients, concomitant diseases, systemic treatments and doses, response to pemphigus treatment, COVID-19 vaccine status, COVID-19 history, and prognosis were recorded retrospectively from the patient's files.

The cumulative prednisolone dose during the follow-up period was manually calculated retrospectively for each patient based on the patient records. Monthly prednisolone doses were calculated by dividing the cumulative prednisolone dose by the number of months followed.

Clinical data were evaluated after the approval of the local noninterventional study ethics committee (Date: August 31, 22; Number: 2022/28-03).

Statistics

Statistical analyses were performed using the IBM SPSS version 26.0.0 (IBM Corporation, Armonk, NY, USA) for Windows. Student's *t*-test or Mann–Whitney *U* test was used for continuous variables, as appropriate. Chi-square or Fisher's

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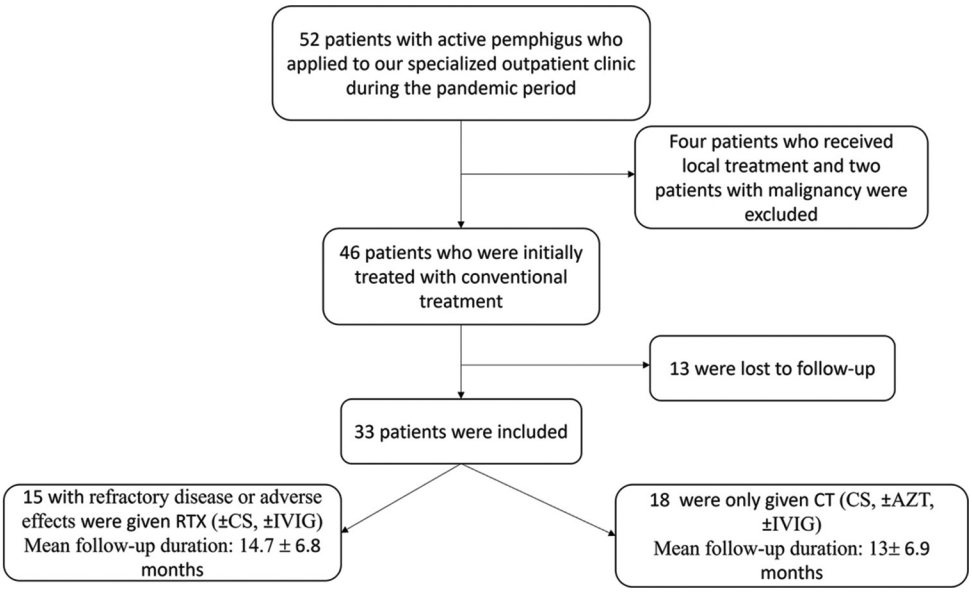


Figure 1: Flow chart. RTX: Rituximab, CS: Corticosteroid, IVIG: Intravenous immunoglobulin, AZT: Azathioprine.

exact test was used when the variable was categorical. The normality distribution of continuous variables was evaluated using Shapiro–Wilk's test. Odds ratios with 95% confidence intervals (CI) were determined using univariate logistic regression. All tests were two-tailed and were considered statistically significant for $P < 0.05$.

Results

In this study, 33 patients with pemphigus who received immunosuppressive treatments due to active disease and followed up for an average of 13.8 ± 6.8 months (range: 1–26 months) were evaluated. Twenty-two of the patients (66.7%) were female and the mean age was 50 ± 15 years with a range of 10–75 years. The baseline mean PDAI score of the patients was 37 ± 34 (range: 4–168).

Thirty-two of 33 patients had been receiving systemic corticosteroids for their pemphigus in the pandemic. One patient who had a history of steroid-induced avascular necrosis could not take prednisolone and was administered rituximab. Steroid-induced psychosis occurred in one female patient therefore, her steroid was discontinued in 2 months.

The vaccine types of the patients were BNT162b2 mRNA in 7 patients, Sinovac in two patients, and both in five patients. A single dose of 500 mg rituximab was administered to 5 of 15 patients for relapse of disease or prevention.

The detailed patient characteristics and the comparison of treatment results between the rituximab and conventional treatment groups are presented in Table 1. The group receiving rituximab treatment and the group receiving conventional treatments were similar in demographic and clinical features, except pemphigus disease duration was statistically longer in the rituximab group than in the conventional treatment group (*P*: 0.01). The mean PDAI activity scores were significantly reduced after treatment in both rituximab and conventional treatment groups (*P*: 0.001, $P < 0.001$; respectively).

In the rituximab group, the monthly mean prednisolone dose after treatment was significantly reduced compared to the monthly prednisolone dose before treatment ($P < 0.001$). The monthly mean prednisolone dose after rituximab treatment was significantly lower than the monthly mean prednisolone dose in the conventional group (*P*: 0.002).

The odds ratios of pemphigus endpoints were not statistically significant between the rituximab and conventional treatment groups [Table 2].

During the follow-up, COVID-19 PCR positivity was detected in 10 patients (30%), and COVID-19 pneumonia was confirmed with computerized tomography in one patient. There was no statistically significant difference in the relative odds of COVID-19 positivity or death between the rituximab and conventional treatment groups (3.06 [95% CI: 0.68–13.79]; 0.57 [95% CI: 0.05–7.00], respectively). Three patients had severe infections requiring hospitalization and intensive care unit. One patient (1/7, 14.3%) in the rituximab group and 2 patients (2/4, 50%) in the conventional treatment group died from SARS-CoV-2. Of them, one patient had respiratory disease, diabetes mellitus, and cardiovascular disease, one had diabetes mellitus and cardiovascular disease and one had only diabetes mellitus. Two of the patients who died from SARS-CoV-2 were vaccinated against COVID-19 under corticosteroid therapy. Demographic features and disease characteristics of 11 pemphigus patients at the time of COVID-19 infection are given in Table 3.

Discussion

Our study demonstrated that rituximab therapy is effective for treatment-resistant moderate-to-severe pemphigus

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Table 1: Comparison of the patient characteristics and treatment results between rituximab and conventional treatment groups

	Rituximab group (± corticosteroid, ± IVIG) (*n*=15), *n* (%)	Conventional treatment group (corticosteroid, ± azathioprine, ± IVIG) (*n*=18), *n* (%)	*P*
Sex			
Female	12 (80)	10 (55.6)	0.138*
Male	3 (20)	8 (44.4)	
Age (years), mean	52 (10–66), 45±16.3	52 (29–65), 54±12.5	0.078†
Disease duration (months)	14 (1–108), 31±36	3.5 (1–74), 8.8±16.6	0.01‡
Diabetes	4 (26.7)	5 (27.8)	>0.99§
Respiratory disease	0	3 (16.7)	0.23§
Cardiovascular disease	5 (33.3)	3 (16.7)	0.41§
Smoking	2 (13.3)	3 (16.7)	>0.99§
COVID-19 vaccine type	14 (93.3)	16 (88.9)	>0.99§
Sinovac	2 (13.3)	4 (22.2)	
BioNTech	7 (46.7)	5 (27.8)	
Both	5 (33.3)	7 (38.9)	
IVIG therapy	7 (46.7)	3 (16.7)	0.12§
Baseline PDAI score	31 (9–168)	34 (4–109)	0.69‡
Severity of pemphigus			
Mild		3 (16.7)	
Moderate	6 (40)	6 (33.3)	
Severe	9 (60)	9 (50)	
Posttreatment PDAI score	0 (0–25)	4 (0–25)	0.55‡
COVID-19 positivity	7 (46.7)	4 (22.2)	0.138*
Death	1 (14.3)	2 (50)	NA

*Pearson Chi-square, §Fisher's exact test, †Student's *t*-test, ‡Mann–Whitney *U*. NA: Nonapplicable, IVIG: Intravenous immunoglobulin, PDAI: Pemphigus disease area index

Table 2: COVID-19 infection and pemphigus endpoints in the treatment groups

	Rituximab (± corticosteroid, ± IVIG) (*n*=15)	Conventional (corticosteroid, ± azathioprine, ± IVIG) (*n*=18)
COVID-19 positivity		
n (%)	7 (46.7)	4 (22.2)
OR (95% CI)	3.06 (0.68–13.79)	Reference
Death		
n (%)	1 (6.7)	2 (11.1)
OR (95% CI)	0.57 (0.05–7.00)	Reference
Complete remission off therapy		
n (%)	5 (33.3)	3 (16.7)
OR (95% CI)	2.50 (0.49–12.87)	Reference
Complete remission on therapy		
n (%)	3 (20)	8 (44.4)
OR (95% CI)	0.31 (0.07–1.50)	Reference
Partial remission on minimal therapy		
n (%)	5 (33.3)	2 (11.1)
OR (95% CI)	4.00 (0.65–24.69)	Reference
Relapse		
n (%)	1 (6.7)	3 (16.7)
OR (95% CI)	0.36 (0.03–3.85)	Reference

IVIG: Intravenous immunoglobulin, PDAI: Pemphigus disease area index, OR: Odds ratio, CI: Confidence interval, IVIG: Intravenous immunoglobulin

vulgaris patients during the COVID-19 pandemic. Although statistically not significant, the median post-treatment PDAI activity score in the rituximab group was lower than in the conventional treatment group. In addition, the frequency of patients who achieved complete remission off therapy was higher in the rituximab group than in the conventional treatment group although the difference was not statistically significant. Agarwal *et al*. determined that rituximab was more

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Table 3: Demographic and clinical characteristics of pemphigus patients diagnosed with COVID-19

Patient number	Sex/age	PDAI	Pemphigus treatments during the COVID-19				COVID-19 vaccination history	COVID-19 pneumonia	Comorbidities	Antiviral therapy/ antibiotics for bacterial super infections	Severity
			Prednisolone (mg)	Azathioprine (mg)	Rituximab, timing of COVID-19 infection postrituximab (days)	IVIG					
1	Female/34	50	20	No	No	No	Three doses of BNT162b2 mRNA	No	No	No/no	No hospitalized, no limitations on activities
2	Female/75	4	15	100	No	No	Under prednisolone, two doses of Sinovac	Yes	RD, DM, CVD	No/no	Death
3	Female/58	18	50	75	No	No	Two doses of BNT162b2 mRNA	Yes	DM	No/no	Death
4	Male/61	49	80	75	No	No	Two doses of Sinovac, two doses of BNT162b2 mRNA	No	No	No/no	No hospitalized, limitation on activities
5	Female/54	7	10	75	No	No	Under prednisolone, two doses of Sinovac, two doses of BNT162b2 mRNA	No	No	No/no	No hospitalized, limitation on activities
6	Female/65	21	2.5	No	164	No	Under prednisolone, two doses of Sinovac, one dose of BNT162b2 mRNA	Yes	DM, CVD	No/yes	No hospitalized, limitation on activities
7	Male/60	32	10	No	164	Yes	Under prednisolone, two doses of BNT162b2 mRNA	Yes	DM, CVD	No/yes	Death
8	Female/10	168	22.5	No	5	Yes	No	Yes	Phenylketonuria	No/yes	Hospitalized, not requiring supplemental oxygen
9	Female/36	9	40	No	5	No	Three doses of Sinovac	Yes	No	No/no	No hospitalized, limitation on activities
10	Female/30	10	No	No	14	No	Two doses of BNT162b2 mRNA	No	No	No/no	No hospitalized, no limitations on activities
11	Female/55	20	No	No	96	No	Under prednisolone, two doses of Sinovac, 2 doses of BNT162b2 mRNA	No	No	No/no	No hospitalized, no limitations on activities

PDAI: Pemphigus disease area index, IVIG: Intravenous immunoglobulin, RD: Respiratory disease, DM: Diabetes mellitus, CVD: Cardiovascular diseases

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effective than conventional treatments in terms of decreasing prednisolone intake in patients despite their refractory disease.[13] In line with these findings, the monthly mean prednisolone dose significantly decreased after rituximab therapy in our treatment-resistant patients. We also showed the efficacy of rituximab in patients with more severe disease; the median baseline PDAI score was higher in our patients in the rituximab group than in the patients of Agarwal *et al*. (31 [9–168] vs. 20 [12–44]). Perifani *et al*. reported the efficacy of rituximab in patients with refractory pemphigus whose mean baseline PDAI score was 41 like the patients in our study (41.6 ± 40).[14] One of the differences between our study and these two studies was IVIG usage in our patients. Seven of 15 patients in the rituximab group were already on IVIG treatment as a steroid-sparing agent and continued after rituximab infusion to treat pemphigus and maintain normal immunity. The possible synergistic effects of rituximab and IVIG may have contributed to the remission of our patients in the rituximab group. The efficacy of a combination of rituximab and IVIG in patients with refractory pemphigus has also been demonstrated in previous studies.[15,16]

Our study did not determine a statistically significant difference in the relative odds of COVID-19 positivity or death between the treatment groups. Among the patients who had COVID-19, one of the seven patients (14.3%) in the rituximab group and two of the four patients (50%) in the conventional treatment group died from severe COVID-19-related complications. Early in the pandemic, postponing rituximab infusions and the effective lowest dose of corticosteroids and steroid-sparing agents (azathioprine and mycophenolate mofetil) were recommended as the principle of pemphigus therapy.[7,17] Subsequently, Moghadam *et al*. reported that a longer interval between the last rituximab dose and the COVID-19 infection was related to decreased disease severity in patients with AIBD. In addition, previous comorbidities and mean prednisolone dosage above 10 mg/day in the last 3 months were determined as significant risk factors for severe COVID-19 disease.[18] A survey-based study also found that rituximab treatment after the onset of the pandemic was associated with a significantly increased risk of COVID-19 infection in patients with AIBD.[19] In another study, rituximab therapy was found to be associated with more severe COVID-19 disease in patients with inflammatory rheumatic and musculoskeletal diseases.[20]

Death from COVID-19 in the conventional treatment group may be related to older age and specific comorbidities, which are known as general risk factors in one of the patients while the other patient was relatively younger and only had steroid-induced DM. These two patients were under corticosteroid and azathioprine therapy when COVID-19 positivity was detected. Previous studies reported that baseline therapy of corticosteroids and thiopurines was associated with an increased risk of severe COVID-19 in patients with autoimmune hepatitis or inflammatory bowel diseases.[21,22] Strangfeld *et al*. reported that besides rituximab therapy, other immunosuppressants such as azathioprine and mycophenolate were also associated with higher odds of death in patients with rheumatic diseases.[23] Combination therapy of azathioprine and prednisolone at a dosage above 10 mg/day was probably the other risk factor leading to severe disease and death in the conventional treatment group.

The lack of difference in the odds ratio of death between the treatment groups may be due to a higher rate of concomitant IVIG usage in the rituximab group than in the conventional treatment group. It has been stated that IVIG can be preferred over other steroid-sparing agents during the COVID-19 pandemic era.[24] The therapeutic effect of IVIG in cases of COVID-19 has been reported.[25] Although there is a potential benefit of IVIG treatment, monthly application to healthcare settings may increase the risk of COVID-19 exposure. Studies are needed to evaluate the effect of subcutaneous administration of immunoglobulin for pemphigus patients, which may be more suitable for limiting clinic visits. The other factor is probably the steroid-sparing effect of rituximab in our patients. Fenizia *et al*. also demonstrated that when compared with healthy controls, both helper and cytotoxic T lymphocytes developed a specific anti-SARS-CoV-2 response, while a lower neutralization ability was detected in patients with pemphigus vulgaris who were treated with rituximab before.[26]

Recently, some encouraging observations on the use of rituximab in the pandemic era have been reported in the literature. Di Altobrando *et al*. administered rituximab to 12 pemphigus patients with a risk of severe disease progression greater than the possible risk of rituximab-induced immunosuppression. No symptoms of COVID-19 infection or positive testing were detected in any of the 12 patients.[27] Koszegi *et al*. reported three pemphigus patients who had COVID-19 vaccinations and developed COVID-19 infection following the rituximab infusions. None of the patients had severe disease and no one needed hospitalization. The authors have recommended a full course of COVID-19 vaccinations and confirmed the humoral response by measuring the patient's SARS-CoV-2 antibodies before rituximab therapy.[28] In a retrospective analysis of a case series with AIBD, no statistically significant difference was found between the rates of SARS-CoV-2 positivity in patients who received rituximab and those who did not receive rituximab (9.1% vs. 12.1%).[29] The reason for the higher COVID-19 positivity in our patients may be that they received health care during the peak of the COVID-19 infection in our hospital. Finally, Özgen *et al*. reported that among seventeen cases of COVID-19 who were treated with rituximab for their pemphigus before, no one needed intensive care or died.[30]

The limitations of our study are the small sample size, the retrospective nature, and the fact that all subjects were from a single center. Another challenge we faced was the heterogeneity of the treatment groups. Because patients received a variety of therapies in addition to rituximab and prednisolone, it was difficult to isolate the impact of rituximab specifically on COVID-19 outcomes. Another

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important limitation of our study is that we did not randomly assign the patients into treatment groups. The patients with pemphigus in the rituximab group were already refractory to prior immunosuppressive treatments, including prednisolone, azathioprine, and IVIG. We also could not confirm the vaccine response by measuring the patients' SARS-CoV-2 antibodies before rituximab therapy. In addition to the above, the rate of lost-to-follow-up, probably due to pandemic conditions, was high in the study. It might lead to underestimating the incidence of the Covid-19 infection. Despite these limitations, our findings can provide valuable real-life data for management of the refractory and moderate-to-severe pemphigus patients in the pandemic conditions.

Conclusions

Our study demonstrated that rituximab treatment was effective and safe for treatment-resistant moderate-to-severe pemphigus patients during the COVID-19 pandemic. The odds ratios of COVID-19 virus positivity and death were not different between the treatment groups. The corticosteroid-sparing effect of rituximab was found to be superior to conventional treatments even if patients were treatment resistant. Given the cumulative steroid dose-related side effects, we suggest that rituximab should be considered for treatment-resistant pemphigus patients with moderate-to-severe disease without delay. Completing a full course of COVID-19 vaccines before immunosuppressive therapy is mandatory to prevent severe infection. If possible, measuring the antibody levels to confirm the vaccine response may be done. IVIG therapy may be beneficial for maintaining normal immunity and synergistic therapeutic effects; however, subcutaneous administration may be preferred for suitable patients to limit visits to health facilities.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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