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Real world evidence: Patients with refractory pemphigus treated with Rituximab

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ABSTRACT

Background: Pemphigus is a group of autoimmune blistering diseases, potentially life-threatening. Rituximab received FDA approval in June 2018 for the treatment of moderate to severe pemphigus vulgaris.
Objectives: To evaluate the efficacy and safety of rituximab in patients with pemphigus, resistant to previous therapies or unable to receive classic immunosuppressive treatment due to serious adverse events or comorbidities.
Materials and methods: Twenty-five patients (9 men, 16 women), mean age 49.4 ± 15.9 years (range 21–74 years), mean disease duration 4 ± 2.7 years (range 0.25–10 years) were included in the study: 19 patients with pemphigus vulgaris and 6 with pemphigus foliaceous. The efficacy of rituximab was evaluated according to the control of disease, retention of remission, disease severity, previous treatments and adverse reactions. During COVID-19 pandemic patients are monitored closely through tele-dermatology.
Results: Twenty-three out of 25 patients had great improvement, 2 out of 25 ceased therapy due to adverse events (arthralgias and dyspnea). Sixteen out of 23 received additional course after 8 months (range 5–60 months). More aged patients presented more frequently adverse events and underwent additional courses ($p = 0.002$). Rituximab was found superior to classic immunosuppressive treatment in terms of efficacy and safety, with larger periods of remission and lower doses of corticosteroids and immunosuppressants. No major adverse events were noticed.
Conclusions: Rituximab is a very effective treatment of pemphigus and, remarkably, superior to classic immunosuppressive treatment.

1. Introduction

Pemphigus constitutes a group of rare autoimmune blistering diseases, characterized histopathologically by intraepithelial blisters and acantholysis, and immunologically by circulating autoantibodies against the surface of epidermal cells. The main lesions are flaccid blisters and erosions of the mucous membrane and the skin [1–3]. Pathophysiologically, the intraepithelial blisters are formed by IgG autoantibodies against two adhesion proteins, desmoglein 3 and/or desmoglein 1 on epidermal keratinocytes [4,5]. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are the two main types of the pemphigus group, with the former affecting the skin and mucous membranes, and the latter affecting only the skin. Pemphigus vulgaris is characterized by autoantibodies against desmoglein 3 and/or desmoglein 1 while pemphigus foliaceus is characterized almost exclusively by autoantibodies against desmoglein 1 [5].

The objectives of the therapeutic management of pemphigus include: 1) the control of the activity of the disease; 2) the healing of the lesions of skin and mucous membranes; and 3) the minimization of the relapses and the adverse effects of the treatment [6]. Although the treatment

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with systemic corticosteroids presents many adverse effects, it has remained the first-line treatment for pemphigus for many years [7–9]. Moreover, therapeutic adjuvants, just as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, cyclophosphamide and high-dose intravenous immunoglobulins (IVIG), can be used for their steroid-sparing effects [1–3].

During the past years, more interest has been shown in shifting from conventional to more targeted therapies for the treatment of autoimmune diseases. Biologic drugs, including monoclonal antibodies such as rituximab, have been used as targeted drug therapy in managing various autoimmune diseases [7–9]. Rituximab is a chimeric monoclonal antibody which targets CD20 surface antigen of B-lymphocytes resulting in their destruction and the inhibition of their evolution to plasmatocytes from which the antibodies are produced from. It was first approved for the treatment of non-Hodgkin's lymphoma in adults and then for rheumatoid arthritis (RA), Wegener granulomatosis and microscopic polyangiitis [7–9]. Moreover, rituximab has gained FDA approval from June 2018 for the treatment of adults with moderate to severe PV, while, in Europe, it was administrated only in experienced centers after written approval from the respective National Drug Organization (in Greece EOF).

The Autoimmune Skin Disease Unit of the 2nd Department of Dermatology and Venereology, National and Kapodistrian University of Athens has been treating patients with pemphigus since 2005, and the use of rituximab was initiated in 2008, with a four-course protocol and a maintenance course 6 months later in steroid resistant pemphigus patients [10]. The purpose of the present study is to evaluate the efficacy and safety of rituximab in patients with pemphigus, resistant to previous therapies or unable to receive classic immunosuppressive treatment due to serious adverse events or comorbidities.

2. Materials and Methods

2.1. Selection of patients

A total of 25 patients with PV and PF admitted, hospitalized and treated with rituximab in our Department from 2008 until September 2018 were enrolled in this study, regardless age, sex and race. The inclusion criteria were proven cases of PV and PF in persons over 18 years of age. This study does not include outcomes from 2018 till now; however, we followed up patients for adverse events but no such events were recorded.

The clinical and demographic features of patients were recorded. Moreover, the duration of the disease, previous treatments and their side effects were recorded from the medical records of the patients. The extend of skin/mucosal involvement was clinically assessed with Pemphigus Disease Area Index (PDAI) score for each patient. Patients were examined in order to assess the severity of the disease according to the PDAI tool, which is internationally accepted as an index for disease activity [11]. The diagnosis was confirmed clinically and histopathologically with skin biopsy from the lesions.

There are two different protocols, one lymphoma and another for RA [8,9]. Rituximab (MabThera-Roche) was given according to the lymphoma protocol, where a total dose of 375 mg/m^2 was administered in four weekly intravenous infusions, as it was already administered in our hospital based on the experience from the Hematologic Department. All patients received therapy with acyclovir (400 mg twice a day) and trimethoprim/sulfamethoxazole (400 mg/80 mg once a day) during the treatment with rituximab and two months after the end of the treatment as a prophylactic treatment against bacterial infections, herpes simplex virus infection and varicella zoster virus infection. Patients who were already treated with systemic corticosteroids and immunosuppressants were tapered later in a period of two to three months, according to the daily dosage of corticosteroids and the duration of their therapeutic use.

The patients selected for the treatment with rituximab met the following criteria: 1) lack of response and dependence on systemic corticosteroids and immunosuppressive treatment; 2) serious side effects caused by the long treatment with systemic corticosteroids and immunosuppressive agents. All patients had written approval from the National Drug Organization for the administration of rituximab. Pregnant women or women during the breastfeeding period were excluded from the study. Previous treatment with rituximab for other reasons, history of malignancy, active and serious infections, such as active Hepatitis B, active Hepatitis C and Interferon-Gamma Release Assay (IGRA) positivity were also exclusive criteria. All patients gave written informed consent. This clinical study was approved by the Scientific and Ethical Committee of the hospital.

2.2. Statistical analysis

Descriptive characteristics of pemphigus cases are presented as proportions for categorical and ordinal variables and as mean ± standard deviation (SD) or median and range for continuous variables. Comparisons between cases and controls were conducted by using chi-square tests for categorical variables and *t*-test or Mann–Whitney test for normally or not normally distributed continuous variables respectively. Statistical analysis of the data was performed with IBM-SPSS® version 24 for Windows.

3. Results

Table 1 depicts baseline features of 25 patients with pemphigus: 9 were males and 16 females with a mean age of 49.4 ± 15.9 years (range 21–74 years). Nineteen patients suffered from PV and 6 from PF with a mean disease duration before rituximab administration of 4 ± 2.7 years (range 0.25–10 years). Median baseline PDAI score was 41 (range 16–122) revealing moderate to severe pemphigus [11]. We also evaluated patients at 3 months and their median PDAI score was 13 (range 7–28). Fig. 1A, B, 2A and 2B show clinical presentations of two patients with PV before and after 3-month treatment with rituximab. Fig. 3A and B depict clinical presentations of one patient with PF before and after 3-month treatment with rituximab. All patients had received systemic corticosteroids (each patient with different prednisone/day dose based

Table 1
Baseline features of 25 patients with pemphigus.

Mean age ± SD (years)	49.4 ± 15.9
Gender (n, %)	
Male	9 (36)
Female	16 (64)
Diagnosis (n, %)	
Pemphigus vulgaris	19 (76)
Pemphigus foliaceus	6 (24)
Mean duration of disease ± SD (years)	4 ± 2.7
Baseline PDAI score (median, range)	41 (16–122)
PDAI score at 3 months (median, range)	13 (7–28)
PDAI score at relapses (median, range)	25 (17–34)
Previous treatments (n, %)	
Systemic corticosteroids	25 (100)
Azathioprine	22 (88)
MMF (mycophenolate mofetil)	12 (48)
IVIg	5 (20)
Cyclosporine	4 (16)
Plasmapheresis	5 (20)
Methotrexate	2 (8)
Cyclophosphamide	2 (8)
Infliximab	1 (4)
Outcome of first session (n, %)	
Improvement	23 (92)
Cease due to adverse events	2 (8)
Time from first session to additional course, median (range) (months)	8 (5–60)
Additional course (n, %)	16 (64)
Number of additional courses (median, range)	1 (1–6)
Reason of additional course (n, %)	
Relapse	11 (44)
Prevention	5 (20)

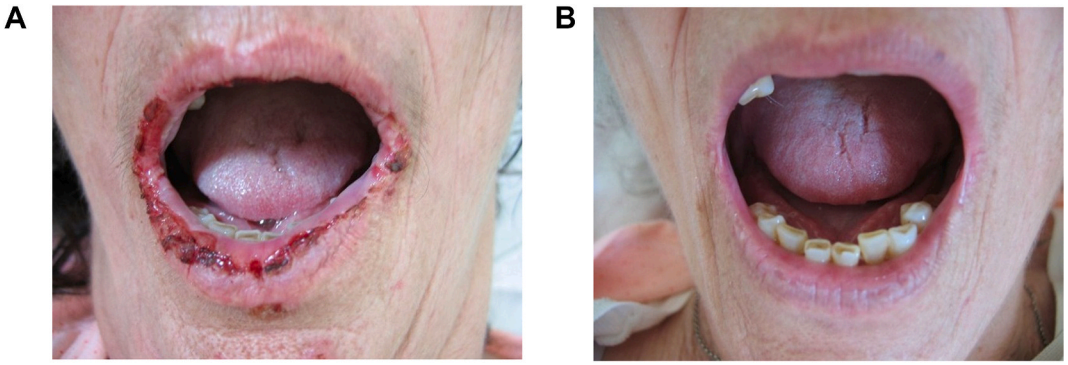

Fig. 1. A & 1B: Clinical presentations of one patient with PV before and after 3-month treatment with rituximab.

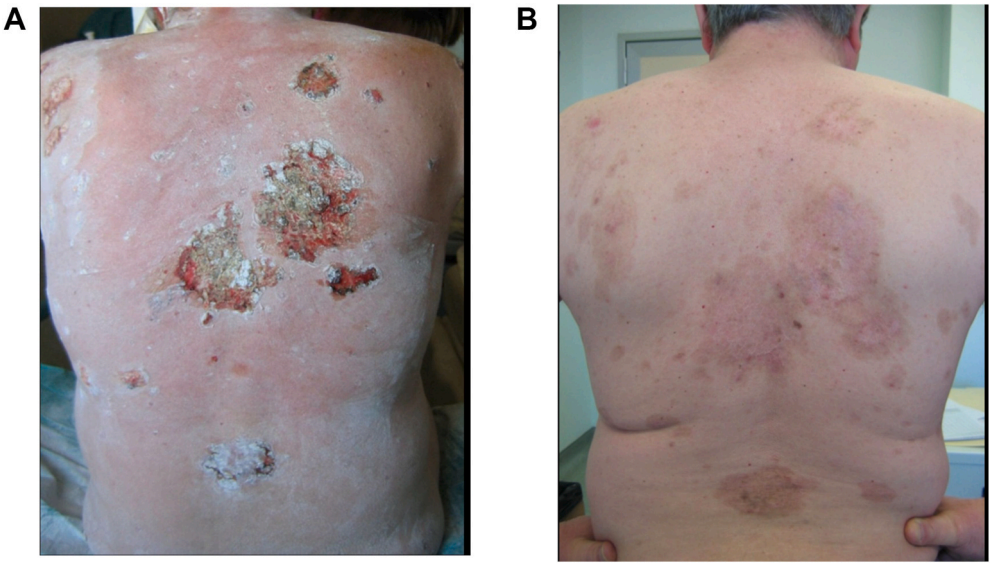

Fig. 2. A & 2B: Clinical presentations of one patient with PV before and after 3-month treatment with rituximab.

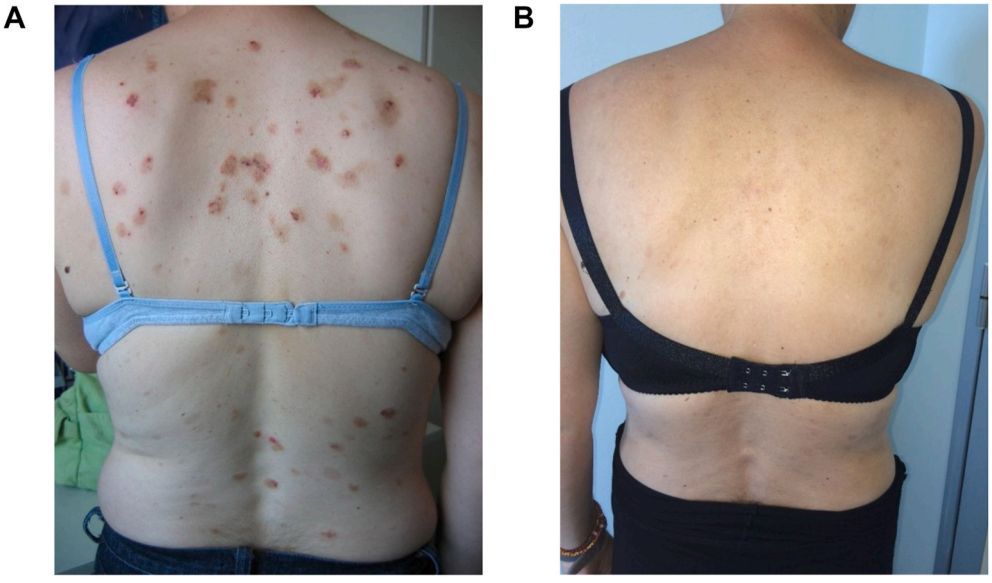

Fig. 3. A & 3B: Clinical presentations of one patient with PF before and after 3-month treatment with rituximab.

on his/her weight) and one or more immunosuppressants, such as azathioprine, mycophenolate mofetil, IVIg and plasmapheresis, without control of the disease, leading to multiple side effects due to the prolonged steroid intake.

Table 2 shows the frequency of the recorded side effects from previous treatments. The two most common adverse effects were osteoporosis/osteopenia and Cushing syndrome, followed by diabetes mellitus and ophthalmologic disorders. We haven't recorded any side effect of any kind (infections including recurrence or relapses from HSV and herpes zoster, etc) at the onset and during the follow up period in patients that completed the treatment with rituximab.

From the total of 25 patients, 23 of them completed the therapy and 2 of them ceased it due to adverse events (one patient presented arthralgias after the second infusion and the other presented dyspnea during the first infusion). All 23 patients had great improvement after the treatment but 16 of them received additional course of 375 mg/m^2 due to relapse (11 patients, 44%) or prevention of relapse (5 patients, 20%), after 8 months (range 5–60 months). Median PDAI score at relapses was 25 (range 17–34).

Generally, there was no association of clinical characteristics and age category (more than 50 years and less than 50 years). However, more aged patients tended to present more frequently osteoporosis ($p = 0.04$), diabetes mellitus ($p = 0.005$) and infections ($p = 0.011$) as side effects of previous treatments, and underwent additional course of treatment ($p = 0.002$). Additionally, there was no association of clinical characteristics and gender. Nevertheless, males presented more often ophthalmologic disorders ($p = 0.048$) and higher PDAI scores than females ($p = 0.06$, borderline statistical significance). Also, pemphigus type was not associated with clinical characteristics and side effects. However, PV patients presented a more frequent association with diabetes mellitus ($p = 0.049$) than patients with PF.

Finally, Table 3 presents all the baseline features of our patients, such as age, gender, duration of pemphigus, PDAI scores, previous treatments and their side effects. Table 4 depicts the treatment features of each patient such as the outcome after the first session, sides effects, the need of additional course or not and the time period between the end of the first session and the additional course.

4. Discussion

In the present study, we have shown that rituximab is a safe and highly effective therapeutic approach in refractory pemphigus with achievement of complete response in almost all patients after the completion of four courses of 375 mg/m^2 of rituximab. Maintenance treatment has been used in the beginning for the relapse prevention (5 out of 25 patients) and later only in some patients (11 out of 25) due to disease relapse [10]. Rituximab was well tolerated; only two patients withdrew due to adverse events which were not relevant to rituximab. One patient had arthralgia during the second course and the other patient presented dyspnea (caused by pulmonary edema) during the first course. Interestingly, more aged patients tended to present more frequently with osteoporosis, diabetes mellitus and infections as side effects and underwent additional course of treatment. Adverse events from previous treatments were more severe, the two most common were osteoporosis/osteopenia and Cushing syndrome, followed by diabetes mellitus and ophthalmologic disorders. No other major or life-threatening adverse events were observed during or after the treatment with rituximab, which is in agreement with the literature [12–17]. Moreover, there were no infections or sepsis in our patients during or after the completion of the treatment.

In our previous study [10], we have investigated the use of rituximab as a maintenance therapy for relapse prevention with an additional course of 375 mg/m^2 administered intravenously in our clinic 6 months after the end of the four-course treatment (without the reintroduction of other systemic medication). We have shown no benefit of using rituximab for relapse prevention, and since then we have administered rituximab only at disease relapse. In our cohort, 5 patients received rituximab for relapse prevention and 11 patients received at least one additional course due to disease relapse, which is in agreement with the results from single centers showing that most patients received at least one additional course [12–14].

Most patients had severe pemphigus; 16 of them had PDAI score between 15 and 45 showing significant pemphigus form, and 9 of them had PDAI score between 45 and 263 revealing extensive pemphigus form [11]. Moreover, more aged patients presented more frequently comorbidities, such as osteoporosis, diabetes mellitus and infections. All these were side effects due to the previous use of systemic treatments. Agarwal et al. showed that rituximab not only decreased prednisolone intake dramatically but it also provided a shorter time to complete remission when compared to classic immunosuppressive treatments [17]. Therefore, rituximab presents an advantage for aged patients, for patients who do not respond to high dose steroids and for patients with other comorbidities.

Rituximab provides clinical improvement with fast initial response, longer disease-free periods compared to classic immunosuppressive therapy. The first report of rituximab therapy in a patient with PV was published in 2002 [18]. Since then, various case reports, case series and studies have shown quite promising results in pemphigus patients who did not respond to standard therapy [19–24], and many patients were treated successfully with rituximab. All these trials have concluded that: 1) rituximab therapy shows an obvious clinical improvement; 2) decreased doses of corticosteroids are needed, and 3) prolonged periods of clinical remission are reported.

Zakka et al. reviewed 42 studies published between 2000 and 2012 on rituximab therapy in a total of 272 patients with refractory pemphigus [25], and found 180 patients treated according to the lymphoma protocol and 92 patients according to the RA protocol. This review showed that patients treated with the lymphoma protocol had lower rates of response, relapse and serious infections [25]. On the other hand, patients treated with the RA protocol had higher rate of response, relapse and infections. Another review by Amber and Hertl showed no significant difference in patients achieving complete remission between patients treated with the lymphoma protocol and those treated with the RA protocol [26]. Moreover, rituximab treatment according to the lymphoma protocol was superior based on the risk for relapse. On the contrary, a meta-analysis from Wang et al. found that high-dose rituximab treatment was associated with a longer duration of complete remission than low-dose rituximab treatment [27]. There was no superiority of the lymphoma over the RA treatment protocol or of high-dose over low-dose rituximab for any other outcome [27].

There are some limitations of our study including its retrospective nature, the small number of patients, the lack of quality of life (QoL) measures, the lack of a control group and the single center trial. Pemphigus diagnosis was based on immunologic (direct and indirect immunofluorescence) and clinical characteristics, as we did not have the possibility of measuring pemphigus autoantibodies against desmoglein

Table 2
Frequency of recorded side effects from previous treatments in 25 patients with pemphigus.

Side Effects	N (%)
Osteoporosis/Osteopenia	11 (44)
Spontaneous fractures	2 (8)
Anxiety and Depression disorders	5 (20)
Hypertransaminemia	3 (12)
Cushing syndrome	11 (44)
Diabetes mellitus	8 (32)
Ophthalmological disorders	8 (32)
Menstrual disorders	2 (12.5) in 16 females
Infections	7 (28)
Hypertension	4 (16)
Secondary adrenal insufficiency	2 (8)

Table 3
Baseline features of 25 patients with pemphigus.

Patient number	Sex	Age (years)	Diagnosis	Duration of disease (years)	Initial PDAI score (0–263)	Previous Treatments	Side events from previous treatments
1	M	55	PV	2.5	122	CS, AZA, MMF, IVIg, plasmapheresis, infliximab	Osteoporosis, Cushing syndrome, DM, anxiety and depression disorders, ophthalmological disorders, infections, hypertension,
2	M	66	PV	1	33	CS, AZA, MMF, plasmapheresis, MTX, cyclophosphamide	Osteoporosis, anxiety and depression disorders, DM, ophthalmological disorders, infections
3	F	74	PV	0.5	34	CS, AZA, MMF	Osteoporosis, DM
4	F	64	PV	1	42	CS, AZA, MMF, cyclosporine	DM, hypertransaminemia, infections
5	F	59	PV	8	16	CS, MMF	Osteoporosis, spontaneous fractures, DM
6	F	51	PV	6	32	CS, AZA, MMF, cyclosporine	Cushing syndrome
7	M	53	PV	7	105	CS, AZA, cyclosporine, plasmapheresis	Cushing syndrome, DM, ophthalmological disorders, infections
8	F	46	PF	2	35	CS, AZA, MMF	Hypertransaminaemia, ophthalmological disorders, hypertension
9	F	32	PV	5	18	CS, AZA, MMF, IVIg, plasmapheresis, cyclophosphamide	Osteoporosis, spontaneous fractures, anxiety and depression disorders, Cushing syndrome, ophthalmological disorders, menstrual disorders
10	F	72	PV	6	35	CS	Cushing syndrome, DM, hypertension
11	M	57	PV	10	34	CS, AZA	Osteoporosis, Cushing syndrome, ophthalmological disorders, infections
12	F	24	PV	4	46	CS, AZA, MMF	Anxiety and depression disorders, Cushing syndrome, ophthalmological disorders, menstrual disorders, hypertension
13	F	55	PV	6	44	CS, AZA	Osteoporosis, Cushing syndrome, infections, secondary adrenal insufficiency
14	M	37	PV	1	90	CS, MMF	Anxiety and depression disorders, ophthalmological disorders
15	M	65	PV	2	50	CS, AZA	DM
16	F	21	PV	6	43	CS, AZA, plasmapheresis	Osteoporosis
17	F	35	PF	2	28	CS, AZA	None recorded
18	M	36	PF	5	34	CS, AZA	None recorded
19	F	67	PV	7	36	CS, AZA, MMF	Osteoporosis, Cushing syndrome, secondary adrenal insufficiency
20	F	23	PV	0.25	99	CS, AZA, IVIg	None recorded
21	F	57	PF	6	49	CS, AZA	Osteoporosis, Cushing syndrome, infections
22	M	52	PF	2	66	CS, AZA, IVIg, cyclosporine	None recorded
23	M	62	PV	0.66	41	CS, AZA, MMF, IVIg	Osteoporosis
24	F	45	PF	4	22	CS, AZA	None recorded
25	F	27	PV	5	47	CS, AZA, MMF, MTX	Cushing syndrome, hypertrtansaminemia

Abbreviations: AZA: azathioprine; CS: systemic corticosteroids; DM: diabetes mellitus; F: female; M: male; MMF; mycophenolate mofetil; MTX: methotrexate; PF: pemphigus foliaceous; PV: pemphigus vulgaris.

Table 4
Treatment features of patients with pemphigus (N = 25).

Patients number	Outcome after first session	Side events after first session	Additional courses	Number of additional courses	Time from first session to additional course (months)	Reason of additional courses
1	Improvement	None	Yes	5	6	Relapse
2	Improvement	None	Yes	6	9	Prevention
3	Improvement	None	Yes	1	6	Prevention
4	Improvement	None	Yes	2	9	Relapse
5	Improvement	None	Yes	4	6	Relapse
6	Improvement	None	Yes	1	9	Prevention
7	Improvement	None	Yes	1	6	Relapse
8	Improvement	None	Yes	4	8	Relapse
9	Stopped treatment	Arthralgia	–	–	–	–
10	Stop treatment	Pulmonary edema	–	–	–	–
11	Improvement	None	No	–	–	–
12	Improvement	None	Yes	1	8	Prevention
13	Improvement	None	Yes	1	10	Prevention
14	Improvement	None	No	–	–	–
15	Improvement	None	Yes	1	60	Relapse
16	Improvement	None	No	–	–	–
17	Improvement	None	Yes	1	8	Relapse
18	Improvement	None	No	–	–	–
19	Improvement	None	Yes	1	8	Relapse
20	Improvement	None	No	–	–	–
21	Improvement	None	Yes	1	8	Relapse
22	Improvement	None	Yes	2	5	Relapse
23	Improvement	None	Yes	1	8	Relapse
24	Improvement	None	No	–	–	–
25	Improvement	None	No	–	–	–

3 and/or 1. However, we present the first study in Greece with real world evidence on the efficacy and safety of rituximab in comparison with previous classic immunosuppressive treatments in refractory pemphigus patients. Additionally, during the COVID-19 Pandemic, our patients are very closely monitored through tele-dermatology. Fortunately, none of our patients is in need of hospitalization nor has shown any sign of relapse. According to the last recommendations, long-term irreversible inhibitors such as rituximab should be avoided during the COVID-19 pandemic [28,29].

In conclusion, our experience from the Autoimmune Skin Diseases Unit shows that rituximab is a safe choice being highly effective as a treatment for refractory pemphigus. Patients treated with rituximab have clinical improvement with fast initial response and longer disease-free periods compared to classic immunosuppressive therapy. Smaller amounts of systemic corticosteroids are needed and fewer side effects from the treatment are recorded.

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Declaration of competing interest

None.

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