ORIGINAL REPORT

Prognostic Factors Predicting Remission Following Rituximab Therapy for Pemphigus Vulgaris

Tal RAVIV[1], Keren PEVZNER[1], Aviv BARZILAI[1,2], Felix PAVLOTSKY[1,3] and Sharon BAUM[1]
[1]Department of Dermatology, Sheba Medical Center, Tel HaShomer, Ramat Gan, affiliated to the Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [2]Institute of Pathology, Sheba Medical Center, Tel HaShomer, Ramat Gan, and [3]Phototherapy Unit, Department of Dermatology, Sheba Medical Center, Tel HaShomer, Ramat Gan, Israel

Pemphigus vulgaris is a chronic autoimmune blistering disease with significant morbidity. Rituximab, approved as its first-line treatment, effectively induces remission. However, few studies have analysed the prognostic factors for improved rituximab outcomes. Therefore, this study aimed to identify such factors in a cohort of pemphigus vulgaris patients. A total of 142 pemphigus vulgaris patients treated with rituximab at Sheba Medical Center, with data encompassing demographics, comorbidities, disease characteristics, and treatment outcomes, were retrospectively examined. Results showed that 61.9% of patients previously treated with mycophenolate mofetil achieved partial remission, whereas only 34.7% achieved complete remission. Patients with diabetes mellitus exhibited a significantly shorter median time to relapse compared with those without. Patients with a disease duration ≤16 months before rituximab therapy exhibited a shorter median time to relapse. Moreover, previous dapsone treatment extended time to relapse. Notably, sex, age at symptom onset and rituximab therapy, ethnicity, comorbidities, skin involvement, weight, rituximab dosing protocol, and other variables were not statistically significant between the complete remission and partial remission groups. These findings highlight the influence of specific patient characteristics and treatment histories on response to rituximab and time to relapse in pemphigus vulgaris patients. Understanding these factors can aid clinicians in predicting treatment outcomes and selecting the appropriate patient population for rituximab therapy.

Key words: pemphigus vulgaris; prognosis; rituximab.

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Corr: Tal Raviv, MD, Department of Dermatology, Sheba Medical Center, Tel HaShomer, Ramat Gan, Israel. E-mail: tal.raviv7@gmail.com

SIGNIFICANCE

Pemphigus vulgaris is a chronic autoimmune blistering disease that manifests as cutaneous and mucous membrane blisters and erosions. First-line therapy with rituximab has been proven to be effective in inducing remission. Due to the few studies published, this study investigated possible prognostic factors for remission post-rituximab therapy in a cohort of pemphigus vulgaris patients. The findings revealed that a history of diabetes mellitus and a short disease duration before rituximab therapy were associated with a short time to relapse; however, previous dapsone treatment before rituximab therapy extended the time to relapse. These results may serve as a critical resource for clinicians.

Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease characterized by the formation of autoantibodies against intercellular adhesion proteins, which generate an intraepidermal split, manifesting clinically as cutaneous and mucous membrane blisters and erosions (1). If untreated, PV can induce possible complications, including dehydration, undernutrition/weight loss, and possible mortality from secondary infections (2).

Prompt systemic corticosteroid therapy is crucial at disease onset and flare-ups to alleviate symptoms and induce remission, which is maintained using steroid-sparing adjuvant treatments that induce general immunosuppression (3). Targeted therapy with rituximab, a monoclonal anti-CD20 antibody against B lymphocytes, originally indicated for non-Hodgkin's lymphoma (NHL), was used off-label for PV before it gained approval as a first-line therapy in 2018 (USA) and 2019 (EU) (4). Rituximab has demonstrated efficacy in inducing disease remission in PV patients, with studies showing disease control in 90–95% of PV patients within ≤6 weeks of treatment initiation. Complete remission (CR) was observed within 3–4 months, whereas most patients remained on minimal steroid or immunosuppressive therapy (5). Nosrati et al. (6) also reported a remission rate of 74% at 5.5 months after the first rituximab cycle, whereas Sharma et al. (7) reported a CR rate of 83.6% at 5 weeks.

However, despite these results, relapse rates have been observed ranging from 10% at 12 months, to 42% at 18 months, and 55% at 24 months (8). Some patients may experience relapse years later, whereas others might be non-responsive to treatment.

Few studies have analysed prognostic factors for improved outcomes with rituximab treatment. In 2019, Kushner et al. identified factors associated with CR in PV patients post-rituximab therapy. Increasing age (>65 years) significantly elevated the odds of achieving CR off therapy (CROT), a body mass index over 35 decreased the odds of achieving CROT, and lymphoma

dosing correlated with 2.7 fold higher CROT likelihood than rheumatoid arthritis (RA) dosing (9). Saha et al. (10) supported these findings: younger onset age was associated with a worse prognosis regarding disease duration, and Indo-Asian patients exhibited significantly longer disease duration than White-British patients. A retrospective study of 29 patients noted no relapses with the oncologic dose group (lymphoma protocol), compared with the 50% observed in the rheumatologic dose group, further strengthening the findings of Kushner et al. (11). In 2017, a retrospective study by Kim et al. reported that CR rates at 6 months following rituximab treatment were significantly higher with 3–4 infusions per cycle than with 2 infusions per cycle (each infusion dose at 375 mg/m^2) (12). Lunardon et al. (13) reported statistically significantly better outcomes with early rituximab treatment. Cho et al. (14) reported that patients with mucosal lesions exhibited increased relapse risk with rituximab treatment by 4.626 times compared with those without, affirming mucosal involvement as a negative predictor of remission in PV, with or without rituximab treatment.

Given the limited studies on prognostic factors for improved outcomes with rituximab therapy, in this study we aimed to investigate possible prognostic factors for remission in rituximab-treated PV patients.

MATERIALS AND METHODS

This retrospective study included 142 PV patients treated with rituximab at the Department of Dermatology and Dermatology Outpatient Clinic, Sheba Medical Center, Israel. Patient data collected between June 2009 and May 2023 were retrieved from a computerized medical records database. PV diagnosis relied on clinical findings of cutaneous and/or mucosal blisters or erosions consistent with the disease. Confirmatory histopathology demonstrated suprabasal epidermal acantholysis and evidence of intercellular IgG deposits (with or without C3 binding) in the epidermis/epithelium, with a net-like pattern as observed through direct immunofluorescence.

Before rituximab gained FDA approval as a first-line therapy for moderate-to-severe pemphigus vulgaris in 2018 (US) and 2019 (EU), dosing regimens standardly used for NHL and subsequently for RA were implemented in PV (15). In our cohort, dosing regimens changed with time, following prevalent practices. From 2009 to 2013, the NHL regimen comprised weekly intravenous infusions of 375 mg/m2 for 4 consecutive weeks. Since 2014, patients have received the RA regimen, consisting of 2 x 1,000 mg infusions spaced 2 weeks apart. Before treatment initiation, all patients received a detailed explanation concerning the drug (including infection prevention and control measures), underwent clinical and laboratory examinations, and were administered vaccinations/preventive treatments as necessary. All patients received infusions at the Dermatology Day Care Unit in the Department of Dermatology, Sheba Medical Center (16). During follow-up, patients were examined at least once in 3 months by 2 dermatology specialists who documented their clinical status.

The collected data encompassed patient demographics (sex, year of birth, and ethnicity), weight, initial clinical presentation, comorbidities (before PV treatment), and clinical history, including cutaneous/mucosal disease involvement, degree of skin involvement, previous adjuvant therapies, and disease duration before rituximab treatment. Information on the first rituximab course was retrieved, including treatment dates and dosing, clinical response, time to remission, and TTR post-course. Treatment response was defined as complete response (CR), partial response (PR), or no response (NR). The CR and PR groups were further subdivided into CR on therapy (CR ON), CR off therapy (CR OFF), PR on therapy (PR ON), and PR off therapy (PR OFF). "Therapy" was defined as prednisone treatment at a dose of $\leq$10 mg, according to consensus guidelines. NR indicated treatment failure with continued lesion development, extension of old lesions, or failure to heal despite 3 weeks of corticosteroid therapy (0.75–1 mg/kg/day prednisone). A relapse or flare-up was defined as the appearance of $\geq$3 new lesions per month that did not spontaneously heal within 1 week or the extension of established lesions in previously controlled disease cases (17). Another endpoint assessed was the TTR, measured in months from the first day of the rituximab course to the relapse date. The studied rituximab course was the first ever administered to the patients.

This study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (reference number 7172-09-SMC). Informed consent was not required owing to the retrospective nature of the study.

Statistical analysis

Continuous variables are described as means and standard deviations (SD), and categorical variables are presented as proportions and percentages. A comparative analysis was performed between CR and PR groups using Student's *t*-test for continuous variables and Pearson's χ^2 test for categorical variables. An additional comparative analysis was performed between CR OFF, CR ON, PR OFF, and PR ON subgroups using the ANOVA test. Time to first relapse was presented using Kaplan–Meier curves, and *p*-values were calculated using the log-rank test and Cox model for binary and continuous variables, respectively. The multivariable Cox regression model included baseline parameters of sex, age, and variables significant in the univariate analysis. All statistical tests were two-tailed, and *p*-values <0.05 were considered statistically significant. Data were analysed using R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In the cohort of 142 patients, 3 NR patients were excluded from the statistical calculations in the univariate analysis (**Tables I–III**) and the Kaplan–Meier curves representing the TTR (**Figs 1–3**). These 3 patients did not achieve remission by definition and, therefore, did not experience a relapse. Consequently, only the CR and PR groups were subjected to further analyses, leading to a statistical cohort comprising 139 patients.

Patient demographics and clinical characteristics are listed in Table I. Regarding sex distribution, the male-to-female ratio was 0.71:1, distributed as 59 males (41.55%) and 83 females (58.45%). Half of the patients identified as Ashkenazi (50.70%), and approximately one-third were Sephardic (37.32%). Owing to subjective definitions and variability associated with the term "mixed" background, 15 patients falling under this category were excluded from the statistical analysis. Similarly, 1 patient from an Arabic background, owing to the small

Table I. Patient demographics and clinical characteristics (for binary variables)

Parameters	CR OFF ($n=44$)	CR ON ($n=74$)	PR OFF ($n=3$)	PR ON ($n=21$)	p-value
Sex, *n* (%)					
Male	15 (34.1)	33 (44.6)	1 (33.3)	10 (47.6)	0.639
Female	29 (65.9)	41 (55.4)	2 (66.7)	11 (52.4)	
Comorbidities					
Cardiovascular (HTN/IHD/dyslipidaemia), *n* (%)					
Yes	13 (29.5)	30 (40.5)	1 (33.3)	6 (28.6)	0.583
No	31 (70.5)	44 (59.5)	2 (66.7)	15 (71.4)	
Neurological (dementia/CVA/TIA), *n* (%)					
Yes	0 (0)	4 (5.4)	0 (0)	0 (0)	0.286
No	44 (100)	70 (94.6)	3 (100)	21 (100)	
Diabetes mellitus, *n* (%)					
Yes	4 (9.1)	7 (9.5)	1 (33.3)	3 (14.3)	0.542
No	40 (90.9)	67 (90.5)	2 (66.7)	18 (85.7)	
Thyroid, *n* (%)					
Yes	4 (9.1)	9 (12.2)	0 (0)	0 (0)	0.358
No	40 (90.9)	65 (87.8)	3 (100)	21 (100)	
Other autoimmune diseases, *n* (%)					
Yes	0 (0)	4 (5.4)	0 (0)	1 (4.8)	0.46
No	44 (100)	70 (94.6)	3 (100)	20 (95.2)	
Degree of skin involvement					
Scalp, *n* (%)					
Yes	22 (50.0)	39 (52.7)	0 (0)	12 (57.1)	0.316
No	22 (50.0)	35 (47.3)	3 (100)	9 (42.9)	
Face, *n* (%)					
Yes	9 (20.5)	23 (31.1)	0 (0)	8 (38.1)	0.283
No	35 (79.5)	51 (68.9)	3 (100)	13 (61.9)	
Upper limbs, *n* (%)					
Yes	11 (25.0)	19 (25.7)	0 (0)	7 (33.3)	0.645
No	33 (75.0)	55 (74.3)	3 (100)	14 (66.7)	
Lower limbs, *n* (%)					
Yes	14 (31.8)	20 (27.0)	0 (0)	6 (28.6)	0.679
No	30 (68.2)	54 (73.0)	3 (100)	15 (71.4)	
Abdomen, *n* (%)					
Yes	19 (43.2)	32 (43.2)	0 (0)	7 (33.3)	0.417
No	25 (56.8)	42 (56.8)	3 (100)	14 (66.7)	
Back, *n* (%)					
Yes	23 (52.3)	37 (50.0)	0 (0)	12 (57.1)	0.322
No	21 (47.7)	37 (50.0)	3 (100)	9 (42.9)	
Previous adjuvant therapies					
Methotrexate, *n* (%)					
Yes	13 (29.5)	20 (27.0)	2 (66.7)	5 (23.8)	0.478
No	31 (70.5)	54 (73.0)	1 (33.3)	16 (76.2)	
Azathioprine, *n* (%)					
Yes	8 (18.2)	10 (13.5)	1 (33.3)	4 (19.0)	0.73
No	36 (81.8)	64 (86.5)	2 (66.7)	17 (81.0)	
Dapsone, *n* (%)					
Yes	5 (11.4)	24 (32.4)	1 (33.3)	6 (28.6)	0.0812
No	39 (88.6)	50 (67.6)	2 (66.7)	15 (71.4)	
Mycophenolate mofetil, *n* (%)					
Yes	17 (38.6)	24 (32.4)	1 (33.3)	14 (66.7)	0.044
No	27 (61.4)	50 (67.6)	2 (66.7)	7 (33.3)	
Cyclophosphamide, *n* (%)					
Yes	1 (2.3)	2 (2.7)	0 (0)	1 (4.8)	0.934
No	43 (97.7)	72 (97.3)	3 (100)	20 (95.2)	
Plasmapheresis, *n* (%)					
Yes	1 (2.3)	1 (1.4)	0 (0)	4 (19.0)	0.00374
No	43 (97.7)	73 (98.6)	3 (100)	17 (81.0)	
IVIg, *n* (%)					
Yes	3 (6.8)	3 (4.1)	1 (33.3)	1 (4.8)	0.185
No	41 (93.2)	71 (95.9)	2 (66.7)	20 (95.2)	
Cyclosporine, *n* (%)					
Yes	0 (0)	1 (1.4)	0 (0)	2 (9.5)	0.0786
No	44 (100)	73 (98.6)	3 (100)	19 (90.5)	
Adjuvant therapy during rituximab treatment, *n* (%)					
Yes	6 (13.6)	18 (24.3)	1 (33.3)	8 (38.1)	0.102
No	38 (86.4)	56 (75.7)	2 (66.7)	11 (52.4)	
Missing	0 (0)	0 (0)	0 (0)	2 (9.5)	
Rituximab dosing protocol					
Rheumatologic (2 g), *n* (%)	37 (84.1)	55 (74.3)	2 (66.7)	15 (71.4)	0.556
Haematologic (375mg/m^2), *n* (%)	7 (15.9)	19 (25.7)	1 (33.3)	6 (28.6)	
Ethnicity, *n* (%)					
Arab	0 (0)	1 (1.4)	0 (0)	0 (0)	0.633
Ashkenazi	21 (47.7)	38 (51.4)	2 (66.7)	11 (52.4)	
Mixed	5 (11.4)	8 (10.8)	1 (33.3)	1 (4.8)	
Other	0 (0)	0 (0)	0 (0)	1 (4.8)	
Sephardic	18 (40.9)	27 (36.5)	0 (0)	8 (38.1)	
Disease involvement, *n* (%)					
Mucous membranes only (m)	11 (25.0)	20 (27.0)	3 (100)	3 (14.3)	0.0188
Skin (s)	1 (2.3)	3 (4.1)	0 (0)	0 (0)	
Skin and mucous membranes (sm)	32 (72.7)	51 (68.9)	0 (0)	18 (85.7)	
Weight (kg), mean (SD)	71.7 (13.6)	73.1 (11.9)	68.0 (14.9)	76.4 (17.8)	0.541
Median [Min, Max]	67.5 [46.0, 100]	75.0 [48.0, 103]	74.0 [51.0, 79.0]	70.0 [54.0, 115]	
Previous adjuvants, mean (SD)	1.05 (1.26)	1.15 (1.28)	2.00 (2.65)	1.81 (1.60)	0.121
Median [Min, Max]	1.00 [0, 6.00]	1.00 [0, 4.00]	1.00 [0, 5.00]	2.00 [0, 6.00]	
Age at symptom onset, mean (SD)	48.8 (13.0)	50.7 (13.7)	45.0 (18.7)	52.5 (13.5)	0.661
Median [Min, Max]	49.5 [15.0, 71.0]	53.0 [19.0, 79.0]	42.0 [28.0, 65.0]	50.0 [31.0, 83.0]	
Disease duration prior to rituximab, months, mean (SD)	34.7 (40.3)	34.4 (55.8)	54.7 (67.0)	45.6 (62.7)	0.766
Median [Min, Max]	18.5 [1.00, 193]	13.0 [1.00, 288]	18.0 [14.0, 132]	20.0 [1.00, 252]	
Age at first rituximab course, mean (SD)	52.4 (12.8)	54.2 (13.9)	49.8 (14.8)	56.9 (12.2)	0.58
Median [Min, Max]	54.0 [16.3, 74.2]	56.1 [20.6, 80.4]	43.4 [39.3, 66.7]	55.9 [34.0, 85.1]	
Total #comorbidities, mean (SD)	0.477 (0.698)	0.730 (0.816)	0.667 (1.15)	0.476 (0.814)	0.314
Median [Min, Max]	0 [0, 2.00]	1.00 [0, 3.00]	0 [0, 2.00]	0 [0, 3.00]	
Total #skin regions involved, mean (SD)	1.73 (1.62)	1.77 (1.63)	0 (0)	1.90 (1.51)	0.286
Median [Min, Max]	1.50 [0, 5.00]	2.00 [0, 5.00]	0 [0, 0]	2.00 [0, 5.00]	

CR: complete response; PR: partial response; Comorbidities: HTN; hypertension; IHD; ischaemic heart disease; Neurological: CVA: cerebrovascular accident; TIA: transient ischaemic attack; SD: standard deviation.

Table II. Time to relapse based on demographical and clinical variables (binary)

Parameters	True (*n*)	Median TTR (months) = True	False (*n*)	Median TTR (months) = false	*p*-value
Sex (True = male/False = female)	58	17	81	20	0.879
Comorbidities:					
CV (HTN, IHD, dyslipidaemia)	49	15	90	20	0.642
Neurological (dementia, CVA, TIA)	4	12	135	18	0.624
Diabetes mellitus	15	11	124	21	0.001
Thyroid	13	23	126	18	0.96
Other autoimmune disease	5	12	134	20	0.406
Degree of skin involvement:					
Scalp	72	20	67	16	0.728
Face	39	24	100	16	0.232
Upper limbs	37	17	102	20	0.839
Lower limbs	40	20	99	17	0.937
Abdomen	58	20	81	16	0.942
Back	71	18	68	18	0.718
Previous adjuvant therapies:					
Methotrexate	38	15	101	21	0.236
Azathioprine	21	17	118	20	0.462
Dapsone	35	36	104	16	0.025
Mycophenolate mofetil	54	15.5	85	23	0.144
Cyclophosphamide	4	13.5	135	20	0.542
Plasmapheresis	5	38	134	18	0.464
IVIg	8	34	131	18	0.91
Cyclosporine	2	11	137	18	0.433
Adjuvant therapy during rituximab course	32	15	105	20	0.286
Rituximab dose (True = R/False = NHL)	107	18	32	20.5	0.854
Ethnicity (True = S, False = A)	52	18	70	20	0.587
Disease involvement (True = sm/False = m)	99	20	36	16	0.736

TTR: time to relapse; Comorbidities: CV: cardiovascular; HTN: hypertension; IHD: ischaemic heart disease; Neurological: CVA: cerebrovascular accident; TIA: transient ischaemic attack; Dosing protocols: R: rheumatologic dose 2 g; NHL: non-Hodgkin's lymphoma; hematologic dose: 375 mg/m²; Ethnicity: S: Sephardic; A: Ashkenazi. Disease involvement: sm: skin and mucous membranes involved; m: only mucous membranes involved.

sample size, was also excluded. The mean age at PV symptom onset was 50.3 years, whereas the mean age at first rituximab therapy was 56.8 years. One-third of the cohort (35.21%) exhibited cardiovascular comorbidities, including hypertension, ischaemic heart disease, and/or dyslipidaemia. One-tenth (10.56%) of the patients were diagnosed with diabetes mellitus (DM), and 9.15% with thyroid disease upon presentation. Regarding PV disease involvement, 71.13% exhibited skin and mucosal involvement, whereas 26.06% displayed mucosal involvement exclusively. Four patients with solely skin involvement were excluded from the statistical analysis because of the small sample size.

Responses to rituximab therapy according to demographics and clinical variables are presented in Table I. Most patients previously treated with mycophenolate mofetil (MMF) achieved PR (61.9%), whereas only 34.7% achieved CR ($p = 0.0349$). Following stratification into the subgroups CR OFF, CR ON, PR OFF, and PR ON, previous treatment with MMF remained a statistically significant parameter ($p = 0.044$). Similarly, regarding patients who had undergone plasmapheresis, a higher proportion achieved PR (14.3%) than those who achieved CR (1.7%) ($p = 0.0265$). Following the same stratification into the above subgroups, plasmapheresis remained statistically significant ($p = 0.00374$). In addition, the degree of skin involvement measured per patient was also statistically significant ($p = 0.0188$). However, sex,

Table III. Time to relapse based on demographic and clinical variables (continuous)

Parameter	*n*	mean	SD	*p*-value
Weight (kg)	139	72.87	13.49	0.365
# Previous adjuvant treatments	139	1.19	1.32	0.779
Age at symptom onset	139	50.27	13.39	0.188
Disease duration prior to first rituximab treatment (months)	139	34.31	48.83	0.041
Age at first rituximab course	139	53.78	13.34	0.59
Total # comorbidities	139	0.62	0.79	0.159
Total # cutaneous areas involved with PV	139	1.76	1.61	0.62

PV: pemphigus vulgaris. SD: standard deviation.

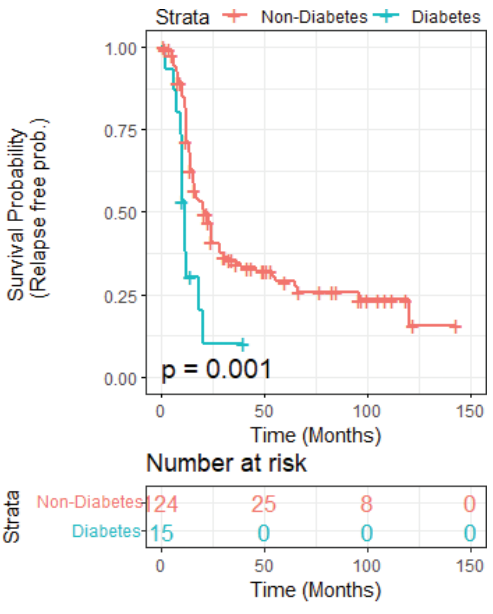

Fig. 1. Kaplan–Meier curve showing time to first relapse following rituximab therapy in pemphigus vulgaris patients with a history of diabetes mellitus.

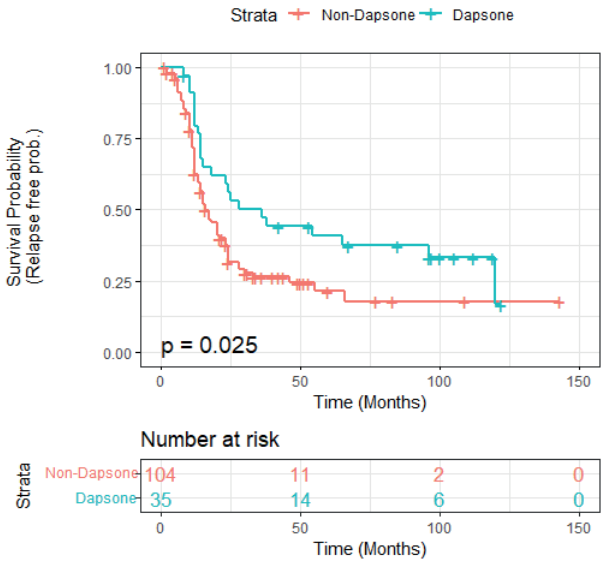

Fig. 2. Kaplan–Meier curve showing time to first relapse following rituximab therapy in pemphigus vulgaris patients previously treated with dapsone.

age at symptom onset and rituximab therapy, ethnicity, comorbidities, weight, rituximab dosing protocol, and other variables (Table I) were not statistically significant between the CR and PR groups.

Table II displays the median TTR calculated according to the binary demographic and clinical variables. Patients with a history of DM exhibited significantly shorter median TTR (11 months) than those without this comorbidity (21 months) ($p=0.001$). Kaplan–Meier curves depicting this comparison are shown in Fig. 1.

Subanalysis of the DM patient group into those on and off steroid therapy showed that steroid therapy did not influence this finding, DM as a comorbidity remained statistically significant, regardless of concomitant steroid therapy ($p=0.002$). Furthermore, patients who received prior adjuvant treatment with dapsone demonstrated a significantly longer TTR (36 months) post-rituximab therapy than patients who did not receive dapsone (16 months) ($p=0.025$). The Kaplan–Meier curve illustrating this comparison is shown in Fig. 2. Student's *t*-test was performed to compare the initial disease severity of patients who received dapsone vs those who did not. Disease severity, depicted in the number of cutaneous areas involved, was not statistically significant between the groups ($p=0.496$). The other parameters (Table II) did not exert a statistically significant influence on TTR.

Table III displays the median TTR calculated for continuous demographic and clinical variables. The only statistically significant parameter was disease duration before rituximab therapy. This parameter is further illustrated in Fig. 3, where it is dichotomized into 2 groups: patients with a disease duration ≤16 months (median disease duration for the full cohort) and those with a disease duration of >16 months before rituximab therapy. Patients with a shorter disease duration (≤16 months) exhibited a shorter TTR than patients with a longer disease duration ($p=0.041$). The Kaplan–Meier curve depicting this comparison is shown in Fig. 3.

Multivariate Cox regression analysis was conducted for the 3 statistically significant variables influencing TTR: DM, prior dapsone treatment, and the disease duration before rituximab, along with sex and age at the start of the rituximab course. The hazard ratio was 2.86 for patients with DM (confidence interval [CI], 1.49–5.5; $p=0.002$), 0.61 for patients with prior dapsone treatment (CI, 0.37–0.997; $p=0.0048$), and 0.79 for the disease duration before rituximab treatment (CI, 0.63–0.98; $p=0.03$) (**Table IV**).

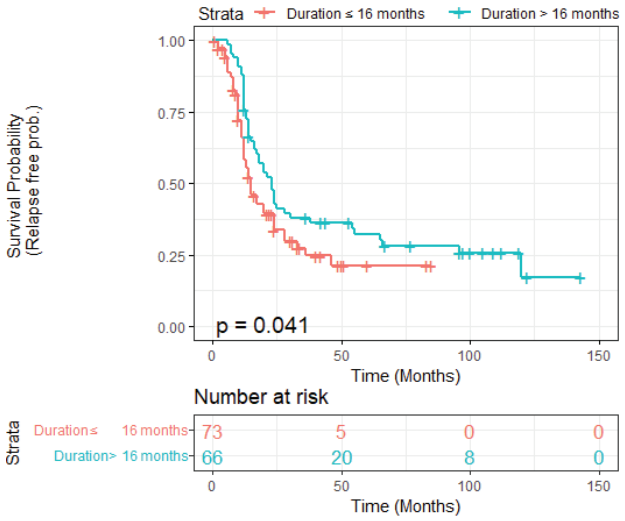

Fig. 3. Relapse-free probability based on disease duration prior to rituximab therapy.

DISCUSSION

This retrospective study, conducted at a prominent tertiary centre in Israel, offers valuable insights into the prognostic factors associated with remission in rituximab-treated PV patients.

Comorbidities

Pemphigus is often associated with other diseases. For instance, Parameswaran et al. indicated a higher incidence of autoimmune thyroid diseases, RA, and type 1 DM in pemphigus patients than in the general population (18).

Table IV. Cox multivariate analysis for statistically significant variables along with sex and age

Parameter	Coefficient	Hazard ratio	*p*-value	Pr(>|z|)
Sex (male/female)	0.06	1.06	0.70	0.778
Age at rituximab course	−0.01	0.99	0.80	0.951
Comorbidities: diabetes mellitus	1.05	2.86	1.49	0.002
Previous treatment with dapsone	−0.50	0.61	0.37	0.049
Disease duration prior to rituximab treatment (months)	−0.24	0.79	0.63	0.033

In a Spanish hospital-based registry encompassing 1,950 PV patients, hypertension (40.19%) and DM(28.57%) emerged as predominant comorbidities, and thyroiditis, among others, was recorded in 0.3% of cases (19). In our study, approximately one-third of the cohort exhibited cardiovascular comorbidities (35.21%), including hypertension, ischaemic heart disease, and/or dyslipidaemia. Additionally, 10.56% of patients had DM, and 9.15% had thyroid disease at the time of presentation. Given the consistent reports, these comorbidities should be considered during the planning and monitoring of PV treatment. This is especially relevant when tapering corticosteroid therapy. For instance, a mode of prevention/exacerbation, such as routine monitoring of glucose levels and blood pressure, coupled with early intervention when values are out of range, can help mitigate the impact of these comorbidities on PV patients.

Previous adjuvant therapies

Upon evaluating the response to rituximab therapy based on previous adjuvant treatments, interesting patterns were observed. Patients previously treated with MMF achieved PR more frequently (61.9%) than CR (34.7%), suggesting that prior MMF therapy may be associated with a slightly reduced likelihood of achieving CR with rituximab. Conversely, in a previous study on repeated rituximab courses in PV patients, we observed reduced relapse rates upon completion of rituximab cycles in patients previously treated with MMF compared with those previously treated with other adjuvants ($p=0.001$) (8). Although the endpoint calculated differed, MMF was associated with a positive disease outcome following rituximab therapy. Conversely, in the current study, MMF was identified as a negative predictor of rituximab success (at the standard dosing protocol of 2g/day). A potential explanation for this finding is the robust immunosuppressive effect of MMF on the disease, which might have led to a state of disease exhaustion before rituximab treatment. Similarly, patients who underwent plasmapheresis before rituximab treatment exhibited a higher proportion of PR (14.3%) than CR (1.7%). However, it is important to approach the significance of this finding with caution, given the limited sample size of patients who underwent plasmapheresis. In contrast, a study involving 155 PV patients treated with a single cycle of rituximab reported that adjuvant plasma exchange or immunoadsorption was associated with an extended TTR (20).

Time to relapse

The analysis of TTR following rituximab therapy revealed significant associations with specific variables. Patients with DM exhibited a significantly shorter TTR (11 months) than those without (21 months). All but 1 patient with DM had non-insulin-dependent diabetes mellitus (NIDDM), which was diagnosed before corticosteroid treatment initiation. This finding suggests that DM may negatively affect long-term remission achieved with rituximab. Notably, there are no previous analyses of diabetes as a prognostic factor for rituximab response in PV. One plausible explanation for our finding could be attributed to the known impaired wound healing and immune responses observed in diabetic patients, which may negatively affect the effectiveness of rituximab in managing the cutaneous wounds associated with PV.

Patients with prior adjuvant treatment with dapsone (at an initial dose of 50–100 mg/day and continued at 100 mg/day) exhibited a significantly longer TTR (36 months) than those without prior dapsone treatment (16 months). This finding suggests that dapsone treatment may have a positive effect on the maintenance of remission post-rituximab therapy. Previous studies have not explored previous adjuvant treatments as prognostic factors in the rituximab response. Theoretically, one could hypothesize that patients who had received prior dapsone treatment in our cohort might have presented with initially milder disease severity, given that dapsone, unlike other immunosuppressive alternatives, is normally administered to individuals with milder PV manifestations. Therefore, following this assumption, these patients would demonstrate a longer disease-free period than patients who had received other immunosuppressive adjuvants. However, Student's *t*-test was performed to investigate this theory and it proved otherwise: there was no statistical difference in the total number of skin areas involved, meaning the 2 groups were not statistically different in terms of initial clinical severity. This disproves the theory that dapsone might have been administered to clinically milder patients. Further research should be conducted to inspect dapsone's effect as a previous adjuvant treatment to rituximab therapy. The multivariate Cox regression analysis further confirmed the association between DM and a shorter TTR, as well as the influence of prior dapsone treatment on a longer TTR.

Another significant finding was the influence of disease duration preceding rituximab treatment on TTR. Patients with shorter disease duration (<16 months) exhibited a shorter TTR, although the *p*-value ($p=0.054$) indicated borderline significance. This finding suggests that initiating rituximab therapy earlier in the disease course may be associated with earlier relapse. This discovery is inconsistent with pertinent published studies. For instance, a recent retrospective study involving 99 PV patients revealed decreased remission rates associated with increased time to rituximab treatment (21). Furthermore, 2 retrospective studies on PV patients by Balighi et al. demonstrated that early administration of rituximab in the treatment of pemphigus results in better outcomes, including a higher remission rate, a longer disease-free period, a lower relapse rate, and a significant reduction

in the requirement for corticosteroids and other immunosuppressants (22, 23). Similarly, Amber et al. (20) and Anandan et al. (24) showed that increased disease duration before rituximab administration correlated with failure to achieve CR and a significantly increased relapse rate. This finding is attributable to 2 possible reasons. First, regarding the natural course of PV, exacerbations occur mostly in the first 2 years, after which disease activity decreases with time (25). Second, it is assumed that patients with prolonged disease duration before rituximab also received prior adjuvant therapies, potentially contributing to better outcomes owing to overall immunosuppression. This emphasizes the importance of recently reported maintenance regimens involving subsequent rituximab administration every 6–12 months following the initial treatment (26, 27). Alternatively, to prevent prolonged B-cell depletion, treatment during exacerbations aligns with the notion that repeated rituximab courses prolong the remission period (8). However, the precise modality awaits further elucidation through randomized controlled studies.

Prior adjuvant dapsone treatment increased the remission period post-rituximab therapy. Conversely, DM may negatively affect the remission period in patients treated with rituximab. Notably, patient sex, age at symptom onset and at rituximab therapy, ethnicity, other comorbidities, degree of skin involvement, weight, and rituximab dosing protocol did not serve as prognostic factors for predicting remission following rituximab therapy. Overall, this study highlights the importance of considering specific factors in the management of PV and the selection of appropriate treatment strategies. Understanding these factors can aid clinicians in predicting treatment outcomes, selecting the appropriate patient population for rituximab therapy, and providing patients with up-to-date information on the success and limitations of rituximab treatment. However, further research with a larger cohort is required to validate these findings. Furthermore, a limitation to our study was its retrospective nature. A disadvantage to this form was the use of the total number of cutaneous areas involved as the disease severity, thus not providing exact disease severity scores. A prospective study with a more standardized severity scoring system would be more informative.

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