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Factors Associated With Complete Remission After Rituximab Therapy for Pemphigus

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IMPORTANCE Rituximab has emerged as a front-line therapy for pemphigus, but prognostic factors for achieving complete remission off therapy (CROT) with oral systemic agents remain unknown.

OBJECTIVES To describe rates of CROT and relapse and identify prognostic factors for achieving CROT after rituximab therapy for pemphigus.

DESIGN, SETTING, AND PARTICIPANTS A single-center, retrospective, cohort study was conducted at the University of Pennsylvania including 112 patients with pemphigus treated with rituximab with at least 12 months' clinical follow-up after the start of rituximab therapy. Multivariate regression analysis of factors predictive of CROT and Kaplan-Meier analysis of disease relapse were conducted. The study included patients treated with rituximab from March 15, 2005, until December 19, 2016. Data analysis was performed from December 2017 to June 2018.

MAIN OUTCOMES AND MEASURES The primary study outcome was CROT after 1 cycle. Secondary study outcomes included rate of CROT or the composite end point of CROT or complete remission on minimal therapy after 1 or more cycle, and median time to relapse. Multivariate regression analysis for prognostic variables for CROT, including age, sex, pemphigus subtype, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), disease duration, and dosing regimen, was performed.

RESULTS A total of 112 patients with pemphigus with median 37.8 months (range, 12.1-130.7) follow-up after rituximab therapy were identified. Of these, 65 were women (58.0%). At the time of first rituximab infusion, median age was 52.3 years (range, 20.0-89.3). Including patients who received multiple cycles of rituximab, 79 patients (70.5%) achieved CROT after a median time of 10.5 months (range, 2.0-49.8), and 36 of 72 patients (50.0%) subsequently experienced relapse after a median of 23.3 months (interquartile range, 10.8-50.4 months). Considering only the first cycle of rituximab, 54 patients (48.2%) achieved CROT. Controlling for age, sex, pemphigus subtype, BMI, and disease duration, patients who received lymphoma vs rheumatoid arthritis dosing were 2.70-fold more likely to achieve CROT (odds ratio [OR], 2.70; 95% CI, 1.03-7.12; $P = .04$). Increasing age was associated with significant increases in achieving CROT (Wald test for trend, $P = .01$), whereas BMI greater than or equal to 35 was associated with a 0.14 OR (95% CI, 0.03-0.63; $P = .01$) for achieving CROT, regardless of the dosing regimen. In multivariate analysis, there was no significant difference in CROT rates with sex (OR, 1.01; 95% CI, 0.42-2.50; $P = .97$), pemphigus subtype (OR, 0.37; 95% CI, 0.09-1.51; $P = .17$), or disease duration (OR, 0.99; 95% CI, 0.98-1.00; $P = .09$).

CONCLUSIONS AND RELEVANCE Lymphoma dosing and older age may be associated with CROT and BMI greater than or equal to 35 may be a negative prognostic factor for CROT after rituximab therapy for pemphigus. These findings help inform clinical expectations and merit evaluation in future prospective clinical trials.

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Pemphigus, caused by antidesmoglein antibodies, is an autoimmune blistering disease affecting skin and mucous membranes.[1] Corticosteroids and oral immunosuppressive agents are mainstays of treatment, but in 2018, the US Food and Drug Administration approved the anti-CD20 monoclonal antibody rituximab for front-line treatment of moderate to severe pemphigus vulgaris. Rituximab depletes CD20-expressing B cells, which impedes autoantibody production and transiently remits symptoms.[2-7] However, the efficacy, safety, and optimal dosing of rituximab in management of pemphigus are uncertain, and prognostic factors are unknown.

Herein, we present a single-center retrospective study of patients with pemphigus who were treated with rituximab. Our relatively large cohort size and long-term follow-up period allowed biostatistical assessment of factors possibly associated with outcome, including age, sex, pemphigus subtype, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), dose regimen, and disease duration before rituximab.

Key Points

Question What are the rates of improvement, safety profile, and prognostic factors for rituximab use in a large cohort of patients with pemphigus at a tertiary care center?

Findings In this cohort study of 112 patients with pemphigus, 48.2% of the patients achieved complete remission off therapy with oral systemic agents after the first cycle of rituximab therapy, 70.5% achieved remission following multiple cycles at a median follow-up time of 10.5 months, and 50.0% of patients experienced relapse after a median of 23.3 months. Lymphoma dose regimen, age greater than 65 years, and body mass index greater than or equal to 35 were significantly associated with rate of complete remission off therapy.

Meaning Long-term outcomes and prognostic factors for complete remission when not receiving oral systemic therapy may inform patient and clinician expectations for rituximab therapy for pemphigus during routine clinical practice.

Methods

Study Patients

This was a retrospective, single-center, cohort study of patients with pemphigus treated with rituximab and followed up for 12 or more months. Eligible patients were identified from treatment logs at the University of Pennsylvania and included all patients with pemphigus vulgaris and pemphigus foliaceus treated with rituximab from March 15, 2005 (the first time a patient with pemphigus was treated with rituximab at the University of Pennsylvania), until December 19, 2016. Pemphigus vulgaris and pemphigus foliaceus were diagnosed by standard criteria, including at least 1 positive immunochemical test (immunofluorescence and/or enzyme-linked immunoassay). Rituximab was administered by a lymphoma dose regimen (375 mg/m^2 weekly for 4 weeks) or a rheumatoid arthritis (RA) dose regimen (1000-mg infusions 14 days apart). The University of Pennsylvania Institutional Review Board approved this retrospective study with waiver of informed consent for deidentified data.

Study Outcomes

Response was defined by standard criteria[8]: complete remission off therapy (CROT), no new lesions for 2 or more months off systemic and topical therapies; complete remission on minimal therapy (CRMT), no new lesions for 2 or more months while receiving minimal doses of systemic and/or topical therapy; partial remission off therapy (PROT), transient new lesions that healed within 1 week without treatment and while off all systemic and topical therapies for 2 or more months; partial remission during minimal therapy (PRMT); and transient new lesions that healed within 1 week during minimal therapy, including topical corticosteroids. The primary study outcome was CROT after 1 cycle. Secondary study outcomes included rate of CROT or the composite end point of CROT or CRMT after 1 or more cycle, and median time to relapse. Serious adverse events were defined by US Food and Drug Administration criteria.[9]

Statistical Analysis

Descriptive statistics were computed for patient and treatment characteristics, as well as rates of clinical outcomes. Univariate analyses were used to investigate statistical associations between CROT post cycle 1 and the ad hoc variables of age, sex, pemphigus subtype, BMI, dose regimen, and disease duration before rituximab therapy. Patients' age, sex, pemphigus subtype, and disease duration prior to cycle 1, as well as patient characteristics that were significantly associated with the primary outcome ($P < .05$) in univariate analyses, were included in multivariate logistic regression analyses. Trend for age was tested after multivariate logistic regression using the Wald test. P values ≤.05 were considered statistically significant. P values were not corrected for multiplicity in this exploratory study, as this could exclude important variables for future clinical study.

Using the Kaplan-Meier method, time to relapse was calculated from the date of the first CROT through the date of relapse; patients were censored at the date of last follow-up. Statistical analyses were conducted from December 2017 to June 2018, using Stata, version 14 software (StataCorp).

Results

Patient Characteristics and Treatments

At the time of first rituximab infusion, the 112 study patients (female:male ratio, 1:4) were a median age of 52.3 years (range, 20.0-89.3) and a median of 18.9 months (range, 2.9-219.8) from onset of pemphigus vulgaris (96 [85.7%]) or pemphigus foliaceus (16 [14.3%]) (**Table 1**). Median BMI was 28.6 (range, 18.6-52.5). Median follow-up from the first rituximab infusion was 37.8 months (range, 12.1-130.7) months. Cycle 1 was the lymphoma regimen in 75 patients (67.0%) and the RA regimen in 37 patients (33.0%). Of the 244 cycles administered for all patients, 154 cycles (63.1%) were lymphoma dose, and 90 cycles

Table 1. Patient Characteristics at Time of First Cycle of Rituximab

Characteristic	Patients, No. (%)
All patients	112 (100)
Age, y	
<45	33 (29)
45-54.9	35 (31)
55-64.9	23 (21)
≥65	21 (19)
Sex	
Male	47 (42)
Female	65 (58)
Diagnosis	
Pemphigus foliaceus	16 (14)
Pemphigus vulgaris	96 (86)
Body mass index[a]	
<35	94 (84)
≥35	18 (16)
Dose regimen, cycle 1	
Lymphoma	75 (67)
Rheumatoid arthritis	37 (33)
Medications at first cycle[b]	
Prednisone, mg/d	96 (86)
≤10	23 (21)
11-20	28 (25)
21-40	23 (21)
41-60	16 (14)
>60	5 (4)
Unknown	1 (1)
Mycophenolate mofetil, mg/d	48 (43)
1000-1500	4 (4)
2000	17 (15)
2500-3000	27 (24)
Azathioprine, mg/kg/d	9 (8)
≤1.25	2 (2)
>1.25-2.0	6 (5)
>2.0-2.5	1 (1)
Doxycycline	8 (7)
Dapsone	7 (6)
Methotrexate, 7.5 mg/wk	2 (2)
Intravenous immunoglobulin	3 (3)
No systemic medications[c]	3 (3)

[a] Calculated as weight in kilograms divided by height in meters squared.

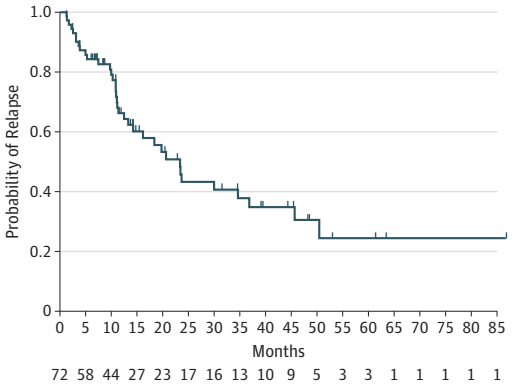
[b] Medications at the time of first rituximab infusion relevant to pemphigus treatment.

[c] Topical medications only.

(36.9%) were RA dose. Fifty-seven patients received 2 or more rituximab cycles: of the 29 patients whose cycle 1 was the RA regimen, 16 also received this regimen in cycle 2, and of the 28 patients whose cycle 1 was the lymphoma regimen, 22 also received this regimen in cycle 2. Dosing regimen was based on clinician preference.

Before receiving rituximab, 109 patients had received systemic therapies. With cycle 1, concomitant medications were mostly prednisone (n = 96) and/or mycophenolate mofetil (n = 48); smaller numbers of patients were receiving other systemic agents or only topical corticosteroids.

Figure. Time to Relapse After Achieving Complete Remission Off Therapy (CROT)



Time to relapse after achieving first CROT (n = 72; median, 23.3 months). Vertical marks indicate censored patients.

Clinical Response After Rituximab Therapy

Of the 112 patients receiving 1 cycle of rituximab, 54 patients (48.2%) achieved CROT, 15 patients (13.4%) achieved CRMT, 10 patients (8.9%) achieved PROT, 14 patients (12.5%) achieved PRMT, and 19 patients (17.0%) were nonresponders. More patients achieved CROT with additional rituximab cycles: 17 patients (15.2%) required 2 cycles, 4 patients (3.6%) required 3 cycles, 4 patients (3.6%) required 4 to 7 cycles, and the remaining 33 patients (29.5%) never achieved CROT. Of the 79 patients (70.5%) who achieved CROT at any time during the study period, this response was reached at a median 10.5 months (range, 2.0 to 49.8 months). Length of follow-up was not a confounding factor for the 33 nonresponders, as their median follow-up from first rituximab infusion was 37.9 months (interquartile range, 29.6-74.1), compared with 37.7 months (interquartile range, 25.4-61.8) for the 79 complete responders.

Complete remission on minimal therapy or CROT as a composite end point (CRMT or better) has been an accepted end point for clinical trials in pemphigus,[8] as it reflects complete healing of skin lesions with minimal doses of oral systemic therapy or no systemic therapies other than rituximab. Ninety-three of 112 patients (83.0%) achieved CRMT or better, including 69 patients (61.6%) after cycle 1, 18 patients (16.1%) after cycle 2, 4 patients (3.6%) after cycle 3, and 2 patients (1.8%) after cycles 4 or 5. Nineteen patients (17.0%) never achieved CRMT or better.

Using Kaplan-Meier analysis, we determined the median time to relapse after the first CROT, setting the time point at which each patient achieved CROT at time 0. Of the 79 patients who achieved CROT at any point during the study period, 7 patients (8.9%) were excluded from relapse analysis because of inadequate recording of dates. Of the 72 patients analyzed, 36 patients (50.0%) experienced relapse within 23.3 months (interquartile range, 10.8-50.4 months) after achieving CROT (**Figure**).

Table 2. Regression Analysis of Rates of CROT After the First Cycle of Rituximab

Characteristic	Univariate Regression Analysis		Multivariate Regression Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y				
<45.0	1 [Reference]		1 [Reference]	
45.0-54.9	2.44 (0.90-6.59)	.08	4.95 (1.47-16.69)	.01
55.0-64.9	2.51 (0.83-7.58)	.10	3.69 (1.02-13.39)	<.05
≥65.0	4.60 (1.42-14.86)	.01	9.74 (2.22-42.62)	.003
Sex				
Male	0.91 (0.43-1.92)		1.01 (0.42-2.50)	
Female	1 [Reference]	.80	1 [Reference]	.97
Disease				
Pemphigus vulgaris	0.79 (0.27-2.35)		0.37 (0.09-1.51)	
Pemphigus foliaceus	1 [Reference]	.67	1 [Reference]	.17
Body mass index[a]				
≥35	0.25 (0.08-0.82)		0.14 (0.03-0.63)	
<35	1 [Reference]	.02	1 [Reference]	.01
Dosing				
Lymphoma	2.65 (1.16-6.05)		2.70 (1.03-7.12)	
Rheumatoid	1 [Reference]	.02	1 [Reference]	.04
Disease duration before cycle 1	0.99 (0.98-1.00)	.12	0.99 (0.98-1.00)	.09

Abbreviations: CROT, complete remission off therapy; OR, odds ratio.

[a] Calculated as weight in kilograms divided by height in meters squared.

Differing rates of CROT were observed in patients who received additional cycles of rituximab to improve response vs those who received additional cycles to treat relapse. Of the 57 patients who received a second cycle and were followed up for 12 or more months, 14 of 39 patients (35.9%) treated to improve response achieved CROT, compared with 14 of 18 patients (77.8%) who had relapsed from prior CROT.

Assessment of Prognostic Factors

In the univariate and multivariate analyses, no significant difference in the rate of CROT was associated with sex (univariate: odds ratio [OR], 0.91; 95% CI, 0.43-1.92; *P* = .80; multivariate: OR, 1.01; 95% CI, 0.42-2.50; *P* = .97), pemphigus subtype (univariate: OR, 0.79; 95% CI, 0.27-2.35; *P* = .67; multivariate: OR, 0.37; 95% CI, 0.09-1.51; *P* = .17), or disease duration before rituximab treatment (univariate: OR, 0.99; 95% CI, 0.98-1.00; *P* = .12; multivariate: OR, 0.99; 95% CI, 0.98-1.00; *P* = .09). In the univariate analysis, the odds of achieving CROT with 1 cycle of rituximab in individuals aged 65 years or older were 4.60-fold higher than with age younger than 45 years (OR, 4.60; 95% CI, 1.42-14.86; *P* = .01). In addition, the lymphoma-dose regimen was associated with increases in the odds of achieving CROT by 2.65-fold compared with the RA-dose regimen (OR, 2.65; 95% CI, 1.16-6.05; *P* = .02). A BMI greater than or equal to 35 decreased the odds (OR, 0.25; 95% CI, 0.08-0.82; *P* = .02) of achieving CROT.

The multivariate analysis suggested that patients who received the lymphoma-dose regimen were significantly more likely to achieve CROT than those who received the RA-dose regimen (OR, 2.70; 95% CI, 1.03-7.12; *P* = .04). In addition, a significantly higher rate of CROT was observed with increasing age (*P* = .01). The ORs of achieving CROT with 1 cycle in individuals aged 45.0 to 54.9 years were greater by 4.95-fold (95% CI, 1.47-16.69; *P* = .01), 3.69-fold (95% CI, 1.02-13.39; *P* < .047) in individuals aged 55.0 to 64.9 years, and 9.74-fold (95% CI, (2.22-42.62; *P* = .003) in those 65 years or older compared with the odds in patients younger than 45 years (*P* = .01 for test for trend). A BMI greater than or equal to 35 decreased the odds (OR, 0.14; 95% CI, 0.03-0.63; *P* = .01) of achieving CROT (**Table 2**).

Serious Adverse Events

During clinical follow-up after first rituximab infusion (median, 37.8 months), 5 patients (4.5%) experienced 5 infectious serious adverse events. Of these, 4 events (80.0%) were attributed to rituximab and 1 event (20.0%) was attributed to rituximab and/or high-dose corticosteroids. One patient treated with 6 cycles of rituximab (RA dose) within 2.5 years developed a perirectal phlegmon requiring surgery and hospitalization. One patient who had received 3 previous cycles of rituximab (lymphoma dose) within 3.5 years was hospitalized for meningitis 7 months after the third cycle and recovered with antibiotic treatment. One patient who received 3 prior cycles (lymphoma dose) within 4.5 years developed a group B streptococcal infection of the lower extremity venous stasis ulcer 9 days into the third cycle, leading to septic shock, with eventual recovery. One patient developed a fever 3 months after the first cycle (lymphoma dose) and was hospitalized with urinary tract infection, which improved with antibiotic therapy. One patient developed *Pneumocystis jirovecii* pneumonia 17 days into the first cycle of rituximab while receiving prednisone, 40 mg/d. This case could have been attributed to high-dose corticosteroids, rituximab, or the combination of the 2 agents.[10-13]

Other serious adverse events that occurred after rituximab, but not directly attributed to the infusions, included takotsubo/stress-induced cardiomyopathy 1 month after a patient's first cycle (lymphoma dose). Another patient developed

a deep venous thrombosis and pulmonary embolus 4 days after the first cycle of rituximab (RA dose), which was attributed to high-dose prednisone.[14]

Discussion

A randomized prospective clinical trial of rituximab showed that first-line use of RA-dose rituximab plus short-term prednisone (0.5-1.0 mg/kg/d) in patients with pemphigus (n = 46), followed by 500-mg maintenance doses of rituximab at months 12 and 18, induced a significantly higher rate of complete remission without corticosteroid therapy by 24 months than high-dose prednisone (1.0-1.5mg/kg/d) alone (n = 44).[5] This landmark study led to US Food and Drug Administration approval of rituximab for pemphigus vulgaris in 2018. However, uncertainties remain regarding efficacy and safety outcomes in patients with pemphigus treated with rituximab as standard-care therapy, as well as prognostic factors for achieving CROT in this clinical setting. We addressed these issues in our large study cohort.

Fifty-four of 112 patients (48.2%) achieved CROT after a single cycle of rituximab. Including patients who received multiple cycles of rituximab, 79 patients (70.5%) achieved CROT. Ninety-three patients (83.0%) exhibited complete healing of skin blisters while receiving no or minimal doses of oral systemic therapies (CRMT or better, which can include patients treated with daily doses of prednisone, up to 10 mg; mycophenolate mofetil, 1500 mg; and/or azathioprine, 1.25 mg/kg). Although not an end point for our study, 89 patients (79.5%) were able to stop oral systemic and topical therapies for 2 or more months with no or minimal disease activity (CROT or PROT). Currently, a composite end point of CRMT or better is considered an acceptable primary end point for clinical trials, but arguably the ability to discontinue all topical and oral systemic therapies with minimal to no disease activity (CROT or PROT) is also a desirable therapeutic goal that should be considered (akin to the clear or almost clear end point used for many dermatology clinical trials).

In regard to prognostic factors for CROT, one of the most notable findings in our multivariate analysis was the superior efficacy of the lymphoma-dose vs the RA-dose regimen. The RA regimen uses a fixed dose of rituximab, whereas the lymphoma-dose regimen is based on body surface area. The rationale for using the lymphoma-dose regimen, which is expected to achieve deeper B-cell depletion in secondary lymphoid tissues than the RA-dose regimen based on both overall dose and schedule of administration,[15] comes from studies suggesting that pemphigus is characterized by an oligoclonal set of nontolerant clones that, once eradicated, are not replaced by new nontolerant clones. This hypothesis is supported by data from longitudinal B-cell repertoire cloning[16] and B-cell spectrotype analysis,[17] which demonstrate elimination of specific pathologic clones in patients who achieve long-term, complete remission.

The multivariate analysis also revealed that older age, and most robustly, age 65 years or older, is significantly associated with achieving CROT after 1 cycle. This advantage may derive from weakened immune systems in elderly patients,[18] which could make remissions of autoimmune reactions easier to achieve.

Body mass index of 35 or greater (moderate to severe obesity) was a negative prognostic factor for achieving CROT after 1 cycle, independent of dose regimen. Reports on patients with RA and cancer have shown mixed results as to whether BMI affects rituximab efficacy.[19,20] Relevant clinical factors may include (1) suboptimal lymphoma dosing of rituximab in those with high BMI with use of the Dubois vs the Mosteller formula[21]; (2) the nonlipophilic nature of rituximab, which causes poor penetration through fat tissue; (3) the obesity-associated increase in adipocytokines, which enhance inflammation and promote autoimmunity; and (4) impaired natural killer cell function in obesity, which may decrease rituximab efficacy via antibody-dependent cellular cytotoxicity.[22] In addition, prolonged corticosteroid therapy to control more refractory pemphigus vulgaris disease activity may have contributed to the association of high BMI with worse prognosis, although corticosteroids are unlikely to be the only cause of moderate to severe obesity in our study population.

Mechanisms for insufficient response to rituximab are not well defined, but could include neutralization from antidrug antibodies, which are observed in up to 56% of patients with pemphigus receiving rituximab therapy[23] and have been associated with direct inhibitory activity,[24] Fc-γ receptor polymorphisms that could affect the efficiency of B-cell depletion,[25,26] or the ratio of short-lived vs long-lived plasma cells that produce pemphigus autoantibodies, the latter of which are not targeted by rituximab. Long-lived plasma cells producing anti-desmoglein antibodies do not appear to occur in most patients with pemphigus, evidenced by the drop in antidesmoglein antibodies to the reference range following rituximab therapy,[5] but could potentially play a role in some patients with refractory pemphigus.

Rituximab has well-known toxic effects attributable to its immunosuppressive effects. The retrospective study design and the study's tertiary referral clinical setting made serious adverse events difficult to reliably capture, since many patients receive primary medical care outside our institution and hence may have experienced serious adverse events that were not reported in the electronic medical record. Nevertheless, serious adverse events were recorded in 5% of our study patients. The data were too limited to compare risks of toxic effects associated with the lymphoma-dose and RA-dose regimens.

Limitations

The present study has several limitations, including its retrospective design, single-center setting, and lack of quantitative measures of disease activity (eg, Pemphigus Disease Area Index or desmoglein enzyme-linked immunosorbent assay values). In addition, although this study comprises what is, to our knowledge, the largest retrospective cohort of patients with pemphigus treated with rituximab, the number of patients is still relatively small.

Conclusions

Lymphoma dosing and older patient age is associated with higher odds of achieving CROT after rituximab therapy in pemphigus. Body mass index greater than or equal to 35 has a negative impact on achieving CROT. The results can help guide patient and physician expectations about clinical outcomes after rituximab therapy and may inform the design of future clinical and translational studies.

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Concept and design: Kushner, Wang, Werth, Payne.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kushner, Wang, Payne.
Critical revision of the manuscript for important intellectual content: Kushner, Tovanabutra, Tsai, Werth, Payne.
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