Rituximab therapy in patients with bullous pemphigoid: A retrospective study of 20 patients

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Background: Bullous pemphigoid (BP) is the most common autoimmune blistering disease requiring treatment with immunosuppressive medications; however, finding a therapy that has a sustained durable response and an acceptable side effect profile has been challenging.

Objective: Our study aimed to evaluate the clinical outcomes of patients with BP treated with rituximab therapy at a single academic center.

Methods: A retrospective chart review was performed on 20 patients who received at least 1 dose of rituximab therapy, either as initial therapy for severe BP or as therapy for recalcitrant disease after having failed conventional immunotherapies.

Results: Within our cohort, 75% of patients (n = 15) achieved remission an average of 169 days following rituximab therapy. There were no rituximab-related deaths and significantly fewer adverse events following rituximab therapy.

Limitations: This study was limited by its retrospective nature, focus on a single academic center, and small sample size.

Conclusion: Use of rituximab therapy demonstrated high rates of remission, steroid-sparing activity, and an acceptable safety profile in our cohort of patients with severe BP or disease refractory to conventional therapies. (J Am Acad Dermatol 2019;81:179-86.)

Key words: autoimmune blistering disease; bullous pemphigoid; relapse; remission; rituximab.

Bullous pemphigoid (BP) is the most common autoimmune blistering disease, resulting in pruritus and blistering from deposition of autoantibodies against BP180 and/or BP230 proteins. BP most commonly affects the elderly, with an increasing incidence in the past 15 years.[1-5] BP can result in significant morbidities and high inpatient burden.[6] Increased rates in mortality have been demonstrated, with potential contributors including increasing age, serious infections, health care disparities, underlying neurologic disorders, and concomitant immunosuppressive therapies.[6-11] Current therapies for BP include conventional immune-suppressing agents such as oral or topical steroids, doxycycline, and dapsone.[12] A Cochrane Database analysis suggests no improved rates of remission with adjuvant agents such as azathioprine or mycophenolate mofetil over prednisone.[13,14] These immunosuppressive medications have side effects and may not improve outcomes, leaving the challenge of finding a therapy with a sustained durable response and an acceptable side effect profile.

There is interest in utilizing rituximab, a chimeric anti-CD20 monoclonal antibody, to achieve sustained remission in BP, particularly with recent US

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Food and Drug Administration approval of rituximab for pemphigus vulgaris.[15] A meta-analysis of 578 patients with pemphigus treated with rituximab showed a rate of serious adverse events of only 3.3%.[16] In BP, case series utilizing rituximab demonstrated increased rates of remission with steroid-sparing activity.[15,16] Reported complications following rituximab have included pneumonias, urinary tract infections, and sepsis, with a review of 16 treated patients demonstrating an infection rate of 3 of 16 (20%), with rare cardiac complications.[15,17] In comparison, 96 patients with BP treated with conventional agents showed an 18% mortality rate within the first year, mostly from infectious complications and contributory underlying neurologic disorders.[18] Our study aimed to evaluate the clinical outcomes of the largest group of patients with BP treated with rituximab therapy at a single academic center.

CAPSULE SUMMARY

- In all, 75% of our cohort of patients with bullous pemphigoid achieved remission after rituximab treatment.
- Patients had fewer adverse events and infections in the period after taking rituximab than before, suggesting an acceptable safety profile. Rituximab is an alternative treatment for recalcitrant bullous pemphigoid.

METHODS

Following institutional review board approval, a retrospective chart review was performed on 94 patients with suspected BP who were seen between June 2012 and July 2017 at the Emory University Department of Dermatology Autoimmune Blistering Disease Clinic. Patients who were older than 18 years, had a histopathologic or serologic diagnosis of BP, and had received rituximab therapy were included in the study. Histologic diagnosis included linear IgG/C3 deposits along the basement membrane zone according to direct immunofluorescence, or staining to the roof on salt-split skin by indirect immunofluorescence, and/or serologically with positive enzyme-linked immunosorbent assay testing for anti-BP180 and anti-BP230 serum autoantibodies using commercially available kits.[19,20] Exclusion criteria included loss to follow-up (defined as <6 months of clinical care following rituximab, with the exception of mortality), data before 2012 (before adoption of the Bullous Pemphigoid Disease Activity Index [BPDAI] scoring system), patients not seen in the blistering clinic, or patients with uncertain diagnoses. One patient who was included had lichen planus pemphigoides.

Overall, 20 patients satisfied the inclusion criteria and were included. These patients received at least 1 round of rituximab therapy, either as initial therapy for severe BP with widespread body surface area involvement based on clinical judgement and a high BPDAI score or recalcitrant disease after having failed conventional immunosuppressive therapies. Rituximab was administered using the protocols for rheumatoid arthritis (RA) (1 g repeated in 2 weeks) or lymphoma (375 mg/m^2 weekly for 4 weeks). Clinical notes were queried for data pertaining to demographics, treatment course, concurrent therapies, clinical scoring (according to the BPDAI and clinical assessment). Blood biomarker study results (presence of BP180, BP230, IgE, CD4, CD8, and/or CD19 and absolute eosinophil count) were collected with each visit (or within 2-3 weeks when available). Medical therapies were recorded as those prescribed at each visit, with the visit before and following rituximab administration considered concurrent.

Clinical status and BPDAI were scored at each visit by using clinical definitions adapted from the consensus statement.[18] Two patients had their BPDAI score assessed post hoc via hospital consultation notes. BPDAI score was assessed clinically at each visit and included erosions/blisters, urticaria/erythema, and mucosal erosions/blisters, for a maximum possible score of 360. BPDAI pruritus score was assessed by utilizing a visual analog scale scored from 0 to 10 in the past 24 hours, week, and month (30 possible points).[21] This scale was adjusted for patients with dementia to include caregiver input as per the BPDAI criteria. Relapse, partial remission, and complete remission were documented as defined in the consensus statement.[21] We reported the pruritus score as a percentage of the 30 possible points to simplify and standardize the statistical analysis.

At each visit patients were divided into 3 subgroups based on disease activity: baseline, flare, or remission. We defined baseline as the first clinic visit to address their BP. Flare was defined as continued development of new lesions or extension of existing lesions despite treatment, and remission was defined as partial or complete remission both while receiving and not receiving therapy as per consensus statement.[21]

Adverse events were queried from descriptions in outpatient clinic notes and discharge summaries from our tertiary medical center and were defined as serious alterations in health requiring

Abbreviations used:

BP: bullous pemphigoid
BPDAI: Bullous Pemphigoid Disease Activity Index
IR: incidence rate
RA: rheumatoid arthritis

hospitalization, including infection, gastrointestinal bleeding, deep vein thrombosis or pulmonary embolism, syncopal events, fractures, altered mental status, and new or recurrent diagnosis of cancer. Hospitalizations for flares of BP without the administration of intravenous antibiotics were considered part of the disease course rather than adverse events.

Statistical method

Statistical analysis was conducted by using SAS software (version 9.4) and SAS macros (developed by Biostatistics and Bioinformatics Shared Resource at the Winship Cancer Institute).[22] The study population included 20 patients with BP, with up to 23 clinic visits for some patients. Descriptive statistics were generated by summary statistics (mean, median, range, and frequency) for baseline characteristics (Table I). Because biomarkers were measured longitudinally over multiple clinical visits, a generalized estimating equation was used to estimate the mean and standard error of biomarkers separated by the corresponding clinical status (baseline, flare, and remission) and to test the difference.[23] A compound symmetry correlation structure among the repeated visits for the same patients was assumed in the generalized estimating equation model. Time to relapse or remission was defined as days from the date of treatment to the earliest date of relapse or remission or the last follow-up date, and the Kaplan-Meier method was applied to estimate the cumulative distribution function of relapse or remission with a 95% confidence limit, with median time to remission or relapse being reported.

RESULTS

A total of 206 visits were reviewed for 20 patients receiving at least 1 course of rituximab (range, 1-3 total courses of rituximab). In all, 19 patients were treated according to the RA protocol and 1 patient was treated according to the lymphoma protocol. This cohort was largely female (70%) and African American (55%), with an average age of 68.9 years at time of first rituximab treatment (range, 36.5-85.1 years) (Table I). In all, 35% of patients (n = 7) had an additional autoimmune disease and 15% (n = 3) had underlying neurologic disease. All patients were receiving concurrent therapies at the time of rituximab therapy, most commonly prednisone (n = 17), with adjuvant therapies including mycophenolate mofetil (n = 6), azathioprine (n = 2), methotrexate (n = 2), doxycycline (n = 3), and dapsone (n = 1). Ten patients were taking prednisone only. All patients were prescribed topical corticosteroids to use as needed.

Of the 20 patients, 17 received 1 course of rituximab, 2 received 2 courses, and 1 received 3 courses (Fig 1). Patients were followed for an average of 508 days after rituximab treatment (range, 131-1248 days). From time of first visit, an average of 231 days (range, 8-926 days) passed before patients received their first course of rituximab (Table I). Kaplan-Meyer curves (Fig 2, *A* and *B*) demonstrated that the median time to remission after rituximab treatment was 196 days (range, 131-418 days), whereas the median time to relapse was 508 days (range, 328-965 days).

In all, 75% of patients (n = 15) achieved durable remission an average of 169 (range 57-418d) days following rituximab therapy (Table I). Eight of the 15 patients attained partial remission, 1 required no adjuvant medication, 3 were maintained with minimal medication (3 with prednisone and 1 additionally with mycophenolate mofetil), and 4 were maintained with adjuvant therapy (3 with mycophenolate mofetil and 1 with methotrexate). The remaining patients attained complete remission: 2 while no longer taking any medications, 4 while taking only minimal medications (1 with mycophenolate mofetil, 2 with prednisone, and 1 with azathioprine), and 1 while taking prednisone and doxycycline. Of the patients achieving durable remission, 60% were no longer taking prednisone (n = 9). The average dose for those still taking prednisone was 7.7 mg (range, 1-20 mg). Of the 15 patients, 2 relapsed an average of 130 days after remission (range, 98-161 days), 1 of whom attained remission again 91 days later without a repeat rituximab course. The other patient had a second relapse requiring a third round of rituximab and has maintained remission for 448 days (Table I and Fig 1).

The other 5 patients did not attain durable remission after rituximab treatment (Fig 1). Of the 5 patients, 1 was lost to follow-up after their first course of rituximab and 3 patients had persistent disease requiring prednisone. One patient had no response to the first course but attained remission 306 days after a second course of rituximab. Unfortunately, she relapsed 126 days later (left boxes in Fig 1).

No cases of mortality were reported during the study period evaluated. There were 23 adverse

Table I. Descriptive statistics and clinical characteristics

Variable	n	%	Mean	Median	Range
Demographics					
Sex					
Male	6	30			
Female	14	70			
Race					
White	8	40			
African American	11	55			
Asian	1	5			
Age at treatment, y			68.9	71.2	36.5-85.1
Other autoimmune diseases*	7	35			
Underlying neurologic diseases†	3	15			
Clinical characteristics					
Days to first RTX course from first visit (n = 20)			231	162	8-926
Days to first remission after first RTX course (n = 15)			169	161	57-418
Days to first relapse after first RTX course (n = 2)			354	354	328-379
Days to first remission after second RTX course (n = 1)			306	306	306
Days to first relapse after second RTX course (n = 1)			126	126	126
Days to second remission after second RTX course (n = 1)			32	32	32
Days to second relapse after second RTX course (n = 1)			284	284	284
Days to third remission after third RTX course (n = 1)			104	104	104
Days remaining in third remission at last visit (n = 1)			448	448	448
Follow-up, d			508	403	131-1248

RTX, Rituximab.
*Hypothyroidism (n = 3), psoriasis (n = 2) ulcerative colitis (n = 1), autoimmune acquired hemophilia (n = 1), and asthma (n = 1).
†History of transient ischemic attack and cerebrovascular accident (n = 2), and neuropathy (n = 1).

events during the pre–rituximab treatment period and 23 adverse events during the post–rituximab treatment period (Table II). Importantly, the incidence rate (IR) of adverse events normalized to rates per person-year before rituximab therapy was 1.836, whereas after rituximab treatment it was 0.827 ($P < .001$).

Additionally, we monitored clinical disease activity indices along with peripheral blood and serologic markers specific to BP (Table III). Notably, BPDAI total activity, BPDAI pruritus score, and anti-BP180 antibody values demonstrated a statistically significant decrease ($P < .0001$) from baseline to remission, suggesting important longitudinal biomarkers to monitor disease activity.

DISCUSSION

BP is a devastating autoimmune blistering disease affecting the elderly, with treatments consisting of conventional immunosuppressive agents with potential for significant risks. Newer treatments that may induce long-term remission and provide steroid sparing are needed. We reviewed data from our cohort of patients with severe or recalcitrant disease despite use of conventional immunosuppression.

In all, 65% of our cohort (13 of 20 patients) experienced remission of their disease after 1 course of rituximab and, as of the time of writing of this article, have remained in remission an average of 410 days following treatment (range, 160-937 days). Of the remaining patients, 1 attained remission but relapsed partly on account of inability to refill his prednisone prescription. Shortly after restarting low-dose prednisone, he achieved remission. Another patient was particularly recalcitrant to treatment and needed 2 more courses of rituximab to attain durable remission after an initial relapse (Fig 1).

In sum, our data show that 15 of 20 patients with BP treated with rituximab (75%) achieved durable remission, with 5 patients requiring adjuvant therapy, 7 receiving minimal therapies, and 3 no longer taking any medications. Additionally, 9 patients were no longer taking prednisone at their last visit, suggesting a steroid-sparing benefit to rituximab therapy. In comparison, 89% of patients (41 of 46) were no longer undergoing therapy 48 months after treatment with a combination of rituximab and prednisone in a prospective open label randomized trial in pemphigus vulgaris.[24]

The adverse event profile in our cohort (Table II) demonstrated a significantly decreased IR in terms of the number of events that were seen before and after rituximab therapy (pre–rituximab therapy IR, 1.836; post–rituximab therapy IR, 0.827; $P < .001$). This is

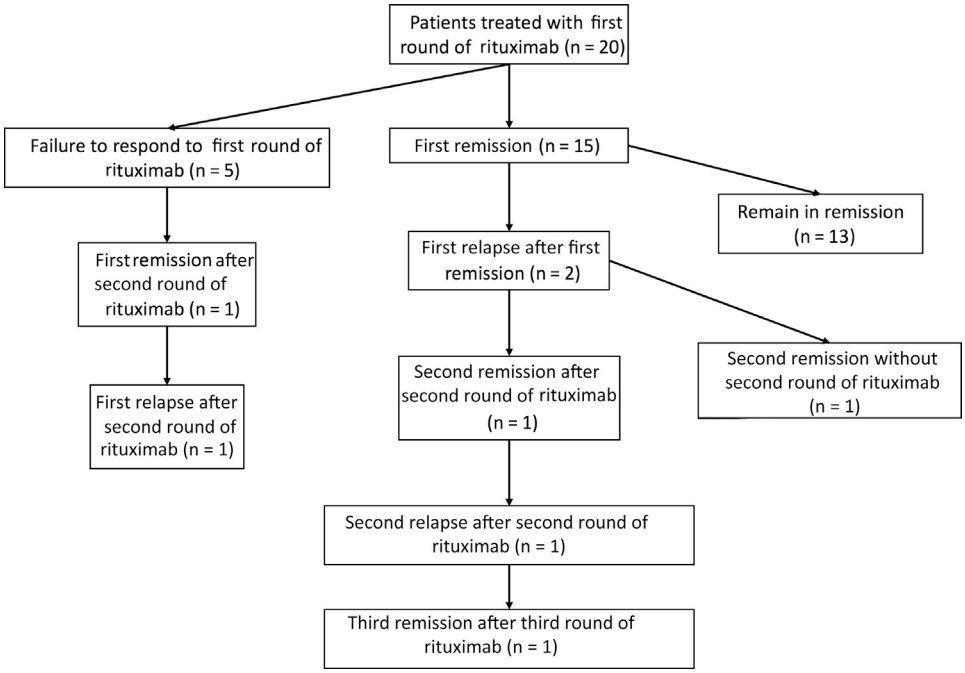

Fig 1. Schematic representation of outcomes after rituximab treatment. A total of 20 patients underwent a first round of rituximab, 5 of whom failed to respond. One of these patients attained remission after a second course of rituximab but relapsed shortly thereafter. The other 15 patients attained remission, and 13 of them remained in remission as of their last visit. Two patients relapsed after their first remission, with 1 attaining a spontaneous second remission without an additional round of rituximab and remaining in remission. The other patient required two more rounds of rituximab, finally attaining and maintaining remission after a third round of rituximab.

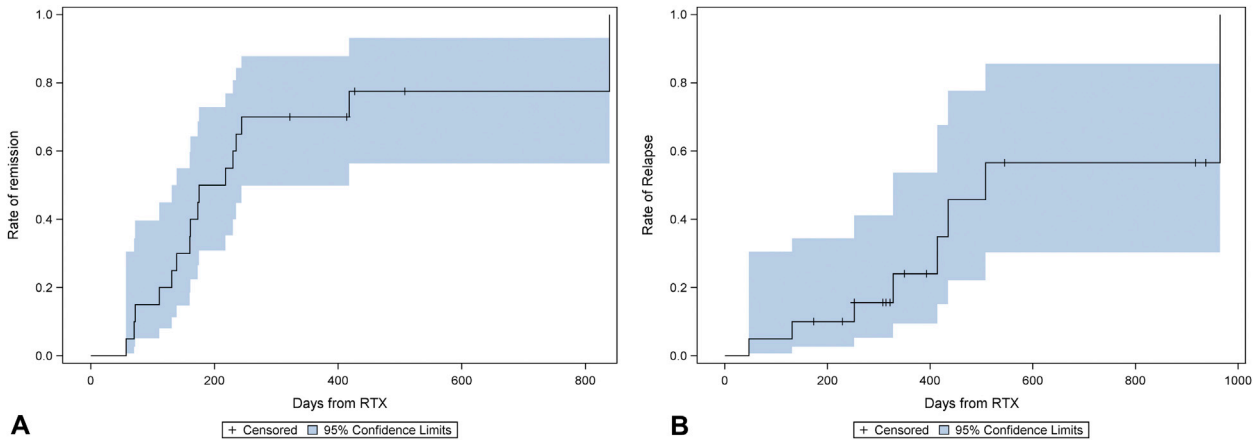

Fig 2. **A**, Kaplan-Meier regression curve demonstrating the time to remission after administration of rituximab (RTX). The median time to remission was 196 days (range, 131-418 days). **B**, Kaplan-Meier regression curve demonstrating the time to relapse after administration of rituximab. The median time to relapse was 508 days (range, 328-965 days).

an important finding, as a major concern of dermatologists administering rituximab to the elderly population is the increased risk of infection following B-cell depletion. In all, 11 infections were noted over a 220-day period in patients who were rituximab naive, and 15 infections were noted over a 508-day period in our patients treated with rituximab. With adjustment for number of events per year, the conventional group had 17 infections whereas the rituximab-treated group had 11 infections per year.

Table II. Adverse events

Variable	Before rituximab	After rituximab
Total events	23	23
Total person-years elapsed	12.5	27.8
Incidence rate*	1.836	0.827
Hospitalization requiring antibiotics	11	15
GI bleed	5	0
DVT/PE	2	0
Altered mental status	3	4
Other†	2	1
Cancer	0	3
		Prostate cancer (12 mo)
		Metastatic breast cancer (9 mo)
		Mucoepidermoid carcinoma (15 mo)

DVT, Deep vein thrombosis; *PE*, pulmonary embolism.
*The test between the 2 incidence rates has a *P* value less than .001 based on a Poisson regression model.
†Before rituximab treatment, hip hematoma requiring 2 units of packed red blood cells, compression fracture; after rituximab treatment, compression fracture.

Table III. Clinical and serologic indices

Variable	Baseline	Flare	Remission	*P* value (GEE)
BPDAI: total activity				
Mean	23.51	29.76	2.81	**<.0001**
SE	5.85	9.06	0.64	
BPDAI: pruritus (VAS%)				
Mean	0.59	0.58	0.16	**<.0001**
SE	0.08	0.08	0.04	
BP180 level				
Mean (U/mL)	95.04	96.65	28.50	**<.0001**
SE	16.54	29.54	8.00	
BP230 level				
Mean (U/mL)	29.94	40.35	21.49	.3397
SE	9.57	15.28	9.07	
IgE level				
Mean (IU/mL)	694.08	337.59	340.03	**.0297**
SE	190.96	113.99	100.33	
Eosinophils				
Mean (abs. count)	0.43	0.47	0.34	.5589
SE	0.12	0.17	0.09	
CD19 level				
Mean (cells/μL)	184.94	88.22	45.99	**.0148**
SE	43.92	80.32	18.88	

Boldface indicated statistical significance.
abs, Absolute; BP180, anti-BP180 autoantibodies; BP230, anti-BP230 autoantibodies; *BPDAI*, Bullous Pemphigoid Disease Activity Index; *GEE*, general estimating equation; IgE, total serum IgE; *SE*, standard error; *VAS*, visual analog scale.

Our cohort did not have any mortalities (for comparison, an 18% mortality rate was observed in patients treated with conventional therapies).[15] There were 3 cancers, which were noted in patients following rituximab therapy. The patient who developed prostate cancer was 72 years old. For comparison, the lifetime risk of a man developing prostate cancer is 11.2%, and 6 of every 10 cases are diagnosed in men aged 65 to 74 years.[25,26] Metastatic breast cancer occurred in 1 patient who had also been previously treated with chemotherapy including cyclophosphamide for autoimmune acquired hemophilia. Long-term studies in RA have not demonstrated increased risks of malignancy following administration of rituximab, but age-appropriate cancer screenings are advised in patients with BP before rituximab therapy.[27] Although our cohort demonstrated decreased infection rates in patients treated with rituximab, only randomized controlled trials can confirm whether rituximab is truly safer when compared with other therapies.

We evaluated commonly used peripheral blood indices following rituximab therapy to evaluate for predictive biomarkers. There were significant decreases in BPDAI total activity, BPDAI pruritus score, and anti-BP180 autoantibody values in remission compared with at baseline and flare (Table III). Our data demonstrate the utility of these biomarkers to monitor disease activity and confirm prior findings.[28,29] Anti-BP180 autoantibody levels in patients achieving remission decreased to an average of 28.5 U/mL. This is consistent with suggested cutoff values of 27 in previous studies including the European treatment guidelines.[30,31] These data suggest that if anti-BP180 autoantibody levels decrease below 27 or 28, it would be reasonable to attempt tapering medications. The difference in BP230 autoantibody level from baseline to remission was not found to be statistically significant, further demonstrating lack of utility for following disease activity.[28]

Total serum IgE levels were significantly decreased in patients in remission compared with baseline (340 vs 694 IU/mL [P = .029]). There is evidence for the role of IgE in patients with BP, as elevated total serum IgE levels have been noted at diagnosis. However, there are conflicting data regarding monitoring changes during therapy and relationship to clinical severity, including urticarial versus blistering phenotypes.[3,32-35]

Peripheral eosinophilia has been reported in patients with BP in about 50% of cases and appears to correlate positively with increasing disease severity.[33,36,37] Additionally, patients with eosinophilia have been reported to be significantly older and have greater palmoplantar disease involvement.[37] Although our data did show a decrease in mean eosinophil count from 0.43 to 0.34, the decrease was not statistically significant. It could have been confounded by the small number of patients in our cohort. We did not correlate disease site with eosinophil counts, but this could be considered in future biomarker studies.

Finally, CD19 levels between baseline, relapse, and disease remission were found to be significantly different (Table III). Previous reports of peripheral B-cell monitoring in RA following rituximab treatments allowed for more accurate prediction of disease relapse.[38] In pemphigus vulgaris, disease relapses tended to occur at the time of B-cell repopulation, and patients with earlier recovery of peripheral CD19 counts (<6 months) had increased rates of relapse than did those in whom repopulation occurred later (>12 months).[39] Further evaluation of the timing and rate of repopulation of B cells monitored by peripheral CD19 in BP may discriminate patients at increased risk of relapse who may benefit from rituximab retreatment.

Our study had several limitations, including a single—academic center cohort, small data set, loss to follow-up, and incomplete data points from the retrospective nature.

In conclusion, our cohort demonstrated a 75% remission rate with a reasonable side effect profile and steroid-sparing activity. We present rituximab as a therapeutic option for patients with BP, along with monitoring of peripheral biomarkers to help guide therapy. Future studies are needed to confirm these data in a larger prospective trial.

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