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Rituximab as a Therapeutic Option in Refractory Vesiculobullous Disorders: A Prospective Clinical Study.

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Abstract

Background: Vesiculobullous disorders represent a heterogeneous group of autoimmune conditions characterized by blister formation and significant morbidity. Conventional immunosuppressive therapies frequently fail to achieve sustained remission, necessitating alternative therapeutic approaches. This prospective clinical study evaluated the efficacy and safety of rituximab in patients with refractory vesiculobullous disorders. ***Methods:*** A single-center prospective study was conducted over 24 months, enrolling 48 patients with refractory pemphigus vulgaris (n=22), pemphigus foliaceus (n=8), bullous pemphigoid (n=13), and mucous membrane pemphigoid (n=5). Patients received rituximab 1000 mg intravenously on days 1 and 15, with clinical assessments at baseline, 3, 6, 12, and 18 months. Primary outcomes included complete remission rates and corticosteroid dose reduction. Secondary outcomes assessed disease activity scores and adverse events. ***Results:*** Complete remission was achieved in 68.8% of patients at 6 months and 81.3% at 18 months. Mean disease activity scores decreased significantly from 42.6 ± 8.3 at baseline to 8.2 ± 4.1 at 18 months ($p<0.001$). Prednisolone doses reduced from 48.3 ± 12.7 mg/day to 5.1 ± 3.8 mg/day ($p<0.001$). Pemphigus vulgaris patients demonstrated superior response rates (86.4%) compared to bullous pemphigoid (69.2%). Mild to moderate adverse events occurred in 29.2% of patients, primarily infusion reactions and infections. ***Conclusion:*** Rituximab represents an effective and relatively safe therapeutic option for refractory vesiculobullous disorders, achieving high remission rates with significant corticosteroid-sparing effects. These findings support rituximab as a valuable addition to the therapeutic armamentarium for autoimmune blistering diseases.

Keywords: Rituximab, vesiculobullous disorders, pemphigus vulgaris, bullous pemphigoid, autoimmune blistering diseases, immunosuppression.

INTRODUCTION

Vesiculobullous disorders constitute a clinically and immunologically diverse group of autoimmune conditions characterized by blister formation affecting the skin and mucous membranes [1]. These disorders, including pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, and mucous membrane pemphigoid, result from autoantibody-mediated destruction of intercellular or basement membrane adhesion molecules [2]. The incidence of pemphigus ranges from 0.76 to 5.0 per million population annually, while bullous pemphigoid affects approximately 2.4 to 23 per million individuals, with significant geographic variation [3].

The pathophysiology of these conditions involves predominantly IgG autoantibodies targeting desmosomal proteins (desmoglein 1 and 3) in pemphigus variants or hemidesmosomal components (BP180 and BP230) in pemphigoid disorders [4]. These autoantibodies trigger complement activation, inflammatory cell recruitment, and subsequent acantholysis or dermal-epidermal separation, manifesting as painful erosions and blisters [5]. The substantial morbidity associated with these conditions, including secondary infections, fluid and electrolyte imbalances, and psychological impact, necessitates prompt and effective therapeutic intervention [6].

Conventional treatment approaches have traditionally relied upon high-dose systemic corticosteroids, often combined with steroid-sparing immunosuppressive agents such as azathioprine, mycophenolate mofetil, or cyclophosphamide [7]. However, approximately 30-40% of patients demonstrate inadequate response or intolerance to these conventional therapies, constituting refractory disease [8]. Furthermore, prolonged corticosteroid exposure engenders significant adverse effects including osteoporosis, diabetes mellitus, hypertension, and increased infection susceptibility [9].

Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen on B-lymphocytes, has emerged as a promising therapeutic alternative in autoimmune blistering diseases [10]. By depleting B-cells, rituximab reduces autoantibody

production and modulates immune dysregulation [11]. Initial case reports and retrospective studies have demonstrated encouraging outcomes, prompting further investigation [12]. Ahmed and colleagues reported 89% complete remission in pemphigus patients treated with rituximab in a multicenter retrospective analysis [13]. Similarly, Colliou et al. demonstrated sustained remission in bullous pemphigoid patients following rituximab therapy [14].

Despite accumulating evidence, prospective data regarding rituximab efficacy across different vesiculobullous disorders remains limited, with most studies focusing exclusively on pemphigus variants [15]. Additionally, optimal dosing regimens, predictors of treatment response, and long-term safety profiles require further elucidation [16]. Comparative efficacy data across different diagnostic subtypes and standardized outcome measures are particularly scarce [17].

The present prospective clinical study aimed to evaluate the therapeutic efficacy and safety of rituximab in patients with refractory vesiculobullous disorders, examining remission rates, disease activity reduction, corticosteroid-sparing effects, and adverse event profiles across multiple diagnostic categories. We hypothesized that rituximab would demonstrate significant therapeutic benefit with acceptable safety profiles in this challenging patient population.

MATERIALS AND METHODS

Study Design and Setting

This prospective, single-center, open-label clinical study was conducted at the Department of Dermatology.

Study Population

Inclusion Criteria:

- Adults aged 18-75 years with confirmed diagnosis of pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, or mucous membrane pemphigoid based on clinical presentation, histopathology, and direct immunofluorescence
- Refractory disease defined as failure to achieve disease control with prednisolone ≥0.5 mg/kg/day for minimum 8 weeks, or relapse requiring prednisolone >20 mg/day after previous taper attempts, or intolerance to at least two conventional immunosuppressive agents
- Active disease with at least 3 new lesions within preceding month
- Adequate hematological, hepatic, and renal function

Exclusion Criteria:

- Previous rituximab exposure
- Active systemic infection or chronic hepatitis B/C infection
- Pregnancy or lactation
- Significant cardiovascular disease
- Malignancy within preceding 5 years
- Absolute neutrophil count <1500/μL or immunoglobulin deficiency

Intervention Protocol

Patients received rituximab 1000 mg intravenously on days 1 and 15, administered over 4-6 hours following premedication with methylprednisolone 100 mg, paracetamol 1000 mg, and diphenhydramine 25 mg. Concomitant prednisolone was continued at baseline doses initially, with tapering initiated upon clinical improvement at investigator discretion. A standardized tapering schedule reduced prednisolone by 10 mg every 2 weeks until reaching 20 mg/day, then by 5 mg every 2-4 weeks.

Outcome Measures

Primary Outcomes:

- Complete remission off therapy: absence of new or established lesions for minimum 2 months while off all systemic therapy
- Complete remission on minimal therapy: absence of new or established lesions for minimum 2 months while receiving ≤10 mg/day prednisolone.

Secondary Outcomes:

- Disease activity assessed using the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)
- Corticosteroid dose reduction
- Time to complete remission
- Adverse events

Assessment Schedule

Clinical evaluations occurred at baseline, 3, 6, 12, and 18 months post-treatment. Assessments included physical examination, lesion counting, ABSIS scoring, photography, and laboratory investigations (complete blood count, comprehensive metabolic panel, immunoglobulin levels, and CD19+ B-cell counts).0

Statistical Analysis

Sample size calculation determined that 44 patients would provide 80% power to detect a 50% remission rate difference with α=0.05. Accounting for 10% dropout, target enrollment was 48 patients. Continuous variables were expressed as mean ± standard deviation and compared using paired t-tests for within-group comparisons and independent t-tests for between-group comparisons. Categorical variables were expressed as frequencies and percentages, analyzed using chi-square or Fisher's exact tests. Kaplan-Meier survival analysis assessed time to remission. Statistical significance was defined as $p<0.05$. Analyses were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY).

RESULTS

Patient Characteristics

Forty-eight patients were enrolled between January 2020 and June 2021, with 46 patients (95.8%) completing the 18-month follow-up. Two patients withdrew due to relocation (n=1) and non-compliance (n=1). The cohort comprised 22 pemphigus vulgaris patients (45.8%), 8 pemphigus foliaceus patients (16.7%), 13 bullous pemphigoid patients (27.1%), and 5 mucous membrane pemphigoid patients (10.4%). Mean age was 48.3 ± 13.6 years, with 27 females (56.3%) and 21 males (43.7%). Mean disease duration prior to rituximab was 3.8 ± 2.1 years. All patients had previously received systemic corticosteroids, with additional exposures including azathioprine (83.3%), mycophenolate mofetil (62.5%), dapsone (41.7%), and cyclophosphamide (12.5%). Baseline mean prednisolone dose was 48.3 ± 12.7 mg/day, and mean ABSIS score was 42.6 ± 8.3.

Efficacy Outcomes

Table 1: Clinical Response Rates at Different Time Points

Outcome Measure	3 Months	6 Months	12 Months	18 Months
Complete remission off therapy	6 (12.5%)	11 (22.9%)	18 (37.5%)	23 (47.9%)
Complete remission on minimal therapy	18 (37.5%)	22 (45.8%)	18 (37.5%)	16 (33.3%)
Partial remission	16 (33.3%)	9 (18.8%)	6 (12.5%)	4 (8.3%)
No response	8 (16.7%)	6 (12.5%)	4 (8.3%)	3 (6.3%)
Total complete remission	**24 (50.0%)**	**33 (68.8%)**	**36 (75.0%)**	**39 (81.3%)**

At 18 months, 81.3% of patients achieved complete remission (either off therapy or on minimal therapy), with 47.9% achieving complete remission off all systemic therapy. Partial remission, defined as ≥50% reduction in disease activity with ongoing new lesion formation, occurred in 8.3% of patients. Three patients (6.3%) demonstrated no response and required alternative therapies.

Table 2: Disease Activity Scores and Corticosteroid Doses Over Time

Parameter	Baseline	3 Months	6 Months	12 Months	18 Months	p-value*
ABSIS total score	42.6 ± 8.3	22.4 ± 6.7	14.3 ± 5.2	10.1 ± 4.8	8.2 ± 4.1	<0.001
ABSIS skin component	28.3 ± 6.1	14.8 ± 5.3	9.2 ± 4.1	6.3 ± 3.7	5.1 ± 2.9	<0.001
ABSIS mucosa component	14.3 ± 4.2	7.6 ± 3.4	5.1 ± 2.8	3.8 ± 2.3	3.1 ± 1.8	<0.001
Prednisolone dose (mg/day)	48.3 ± 12.7	28.6 ± 9.4	15.2 ± 7.3	8.4 ± 5.2	5.1 ± 3.8	<0.001
Number of active lesions	18.7 ± 7.4	7.3 ± 4.8	3.2 ± 2.6	1.4 ± 1.8	0.6 ± 1.2	<0.001

*Compared to baseline using paired t-test

Mean ABSIS scores decreased significantly from baseline (42.6 ± 8.3) to 18 months (8.2 ± 4.1), representing an 80.8% reduction ($p<0.001$). Both cutaneous and mucosal components demonstrated substantial improvement. Prednisolone doses reduced by 89.4%, from 48.3 ± 12.7 mg/day to 5.1 ± 3.8 mg/day ($p<0.001$). Mean time to complete remission was 6.8 ± 2.4 months.

Table 3: Comparative Outcomes by Disease Subtype at 18 Months

Parameter	Pemphigus Vulgaris (n=22)	Pemphigus Foliaceus (n=8)	Bullous Pemphigoid (n=13)	Mucous Membrane Pemphigoid (n=5)	p-value
Complete remission rate	19 (86.4%)	7 (87.5%)	9 (69.2%)	4 (80.0%)	0.412
Mean ABSIS reduction (%)	84.3 ± 8.2	82.1 ± 9.7	74.6 ± 12.3	78.8 ± 10.4	0.046
Prednisolone reduction (%)	91.2 ± 6.8	89.7 ± 7.3	85.4 ± 9.2	87.6 ± 8.1	0.128
Time to CR (months)	6.2 ± 2.1	6.4 ± 1.9	8.1 ± 2.8	7.2 ± 2.6	0.031
Relapse rate	2 (9.1%)	0 (0%)	3 (23.1%)	1 (20.0%)	0.267

Pemphigus vulgaris patients demonstrated the highest complete remission rates (86.4%), though differences across subtypes were not statistically significant (p=0.412). However, ABSIS reduction percentages differed significantly among groups (p=0.046), with pemphigus variants showing superior responses compared to pemphigoid conditions. Time to complete remission was significantly shorter in pemphigus vulgaris (6.2 ± 2.1 months) compared to bullous pemphigoid (8.1 ± 2.8 months, p=0.031).

Safety and Adverse Events

Adverse events occurred in 14 patients (29.2%). Infusion reactions, characterized by fever, chills, and hypotension, occurred in 8 patients (16.7%), all during the first infusion and managed successfully with temporary infusion interruption and symptomatic treatment. Infections developed in 6 patients (12.5%), including upper respiratory tract infections (n=4), urinary tract infections (n=1), and herpes zoster (n=1). All infections resolved with appropriate antimicrobial therapy without treatment discontinuation. No serious adverse events, opportunistic infections, or deaths occurred during the study period.

Laboratory monitoring revealed transient hypogammaglobulinemia (<600 mg/dL) in 11 patients (22.9%) at 6 months, normalizing by 12 months in 8 patients. Complete B-cell depletion (CD19+ count <5 cells/μL) was achieved in 44 patients (91.7%) at 1 month post-treatment, with reconstitution beginning at mean 9.3 ± 2.7 months.

DISCUSSION

This prospective clinical study demonstrates that rituximab represents a highly effective therapeutic option for patients with refractory vesiculobullous disorders, achieving 81.3% complete remission rates at 18 months with significant corticosteroid-sparing effects and acceptable safety profiles. These findings substantially contribute to the expanding evidence base supporting rituximab utilization in autoimmune blistering diseases, particularly across diverse diagnostic subtypes.

The observed complete remission rate of 81.3% in our cohort aligns with previous reports in the literature. Joly and colleagues, in their landmark multicenter randomized controlled trial comparing rituximab with conventional corticosteroid therapy in newly diagnosed pemphigus, reported 89% complete remission at 24 months in the rituximab group [18]. Similarly, a systematic review by Wang et al. examining rituximab efficacy in pemphigus identified pooled complete remission rates of 85.7% across multiple studies [19]. Our slightly lower remission rate may reflect the exclusively refractory nature of our patient population, who had failed multiple prior immunosuppressive therapies, potentially indicating more resistant disease biology [20].

The substantial reduction in disease activity, as evidenced by the 80.8% decrease in ABSIS scores, corroborates findings from previous investigations. Ingen-Housz-Oro and colleagues reported similar magnitude reductions in disease activity scores following rituximab therapy in bullous pemphigoid patients [21]. The parallel improvements in both cutaneous and mucosal components suggest rituximab's efficacy extends across different anatomical manifestations, addressing a critical therapeutic need given the significant morbidity associated with mucosal involvement [22].

The remarkable corticosteroid-sparing effect observed in our study, with 89.4% reduction in prednisolone dosage, represents a particularly clinically significant finding. Prolonged high-dose corticosteroid therapy contributes substantially to morbidity and mortality in vesiculobullous disorder patients [23]. Cianchini et al. demonstrated that pemphigus patients treated with rituximab achieved similar outcomes with significantly lower cumulative corticosteroid exposure compared to conventional therapy [24]. This steroid-sparing capacity potentially mitigates complications including osteoporosis, diabetes, cardiovascular disease, and infection susceptibility that frequently complicate long-term immunosuppression [25].

Comparative analysis across disease subtypes revealed interesting patterns, with pemphigus variants demonstrating superior response rates and more rapid remission compared to pemphigoid conditions. This differential response may reflect distinct immunopathological mechanisms. Pemphigus pathogenesis centers predominantly on IgG4 autoantibodies against desmogleins, with disease activity correlating closely with circulating antibody titers [26]. Rituximab-mediated B-cell depletion directly targets this antibody-producing cellular population. Conversely, bullous pemphigoid demonstrates more complex pathogenesis involving IgG, IgE, and cellular immunity components, potentially explaining the somewhat attenuated response [27]. Nevertheless, the 69.2% complete remission rate in bullous pemphigoid patients remains clinically meaningful, particularly given limited therapeutic alternatives for refractory cases [28].

The safety profile observed in our study compares favorably with reported literature. The 16.7% infusion reaction rate falls within expected ranges, with most reactions occurring during initial infusion and managed successfully with standard protocols [29]. The 12.5% infection rate, while requiring vigilance, appears acceptable given the immunocompromised

status of this patient population receiving concurrent immunosuppression. Importantly, no severe infections, progressive multifocal leukoencephalopathy, or deaths occurred, contrasting with concerns raised regarding rituximab safety in other autoimmune conditions [30].

Transient hypogammaglobulinemia occurred in 22.9% of patients, consistent with previous reports and generally self-limiting [31]. Routine immunoglobulin monitoring allows early detection and intervention if clinically indicated. The mean B-cell reconstitution time of 9.3 months provides valuable data for planning potential retreatment strategies, though the optimal rituximab dosing schedule and retreatment criteria in vesiculobullous disorders remain areas requiring further investigation [32].

Our study possesses several strengths, including prospective design, standardized outcome measures using validated instruments (ABSIS), comprehensive assessment schedule extending to 18 months, and inclusion of multiple vesiculobullous disorder subtypes allowing comparative analyses. However, limitations warrant acknowledgment. The single-center design and relatively modest sample size may limit generalizability, particularly for less common subtypes like mucous membrane pemphigoid. The open-label design introduces potential bias, though objective outcome measures partially mitigate this concern. The 18-month follow-up duration, while substantial, may not capture long-term durability of remission or late adverse effects [33].

Future research should focus on identifying predictive biomarkers for rituximab response, enabling patient selection optimization [34]. Investigations examining optimal dosing regimens, including lower-dose protocols and maintenance strategies, could enhance treatment accessibility and safety [35]. Long-term follow-up studies extending beyond 2-3 years will elucidate remission durability and inform retreatment algorithms [36]. Additionally, comparative effectiveness research examining rituximab versus emerging therapeutic alternatives, including other biologics targeting different immunological pathways, will guide evidence-based treatment sequencing [37].

CONCLUSION

This prospective clinical study demonstrates that rituximab constitutes a highly effective and relatively safe therapeutic option for patients with refractory vesiculobullous disorders across multiple diagnostic subtypes. The achievement of 81.3% complete remission rates at 18 months, coupled with substantial disease activity reduction and remarkable corticosteroid-sparing effects, positions rituximab as a valuable addition to the therapeutic armamentarium for these challenging conditions. The favorable safety profile, characterized predominantly by manageable infusion reactions and minor infections without serious adverse events, supports rituximab's clinical utility in this population.

These findings have important clinical implications, suggesting that rituximab should be considered early in the treatment algorithm for patients demonstrating inadequate response to conventional immunosuppression, rather than reserving it exclusively for severely refractory cases. The differential responses observed across disease subtypes, with particularly robust outcomes in pemphigus variants, may inform individualized treatment planning and patient counseling regarding expected outcomes.

The substantial reduction in corticosteroid requirements represents a critical therapeutic achievement, potentially preventing significant iatrogenic morbidity associated with prolonged high-dose corticosteroid exposure. As the therapeutic landscape for autoimmune blistering diseases continues evolving, rituximab stands as an evidence-supported intervention that meaningfully improves clinical outcomes while enhancing patient quality of life through reduced treatment burden and steroid-related complications.

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