Section: DVL

Original Research Article

EFFICACY AND SAFETY OF LOW-DOSE RITUXIMAB IN THE TREATMENT OF IMMUNOBULLOUS DISORDERS

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Abstract

Background: Blisters arise as a result of autoimmune reactions against skin proteins, which are a hallmark of immunobullous illnesses such as pemphigus and pemphigoid families. Rituximab is a chimeric monoclonal antibody that targets CD20+ B cells. It has become a viable treatment option by depleting B cells, which may reduce the formation of autoantibodies. The aim of this study is to assess the effectiveness and safety of low-dose rituximab in the treatment of immunobullous diseases. **Material and Methods:** Twenty patients were recruited who had been diagnosed with bullous pemphigoid and widespread pemphigus, including pemphigus vulgaris and pemphigus foliaceus. Two weeks apart, the participants were given two 500 mg doses of rituximab. In order to track response and unfavorable occurrences, follow-up assessments were carried out every two weeks for the first three months and then every month for the next year. **Results:** Of the patients in the cohort, nine had pemphigus vulgaris, eight had bullous pemphigoid, and three had pemphigus foliaceus. Fourteen patients were treated for refractory illness, whereas six individuals received rituximab as a first-line treatment. 58% of pemphigus patients had complete remission and 42% had partial remission at the three-month evaluation. For bullous pemphigoid patients, a similar 62% of patients experienced complete remission and the remaining 38% experienced partial remission. A consistent improvement was observed during the 6- to 12-month follow-up period, with 87% of patients with bullous pemphigoid and 66% of patients with pemphigus in complete remission. **Conclusion:** A considerable percentage of patients achieve and sustain total remission with low-dose rituximab therapy, showing a promising safety and efficacious profile in the treatment of immunobullous diseases. These results give patients, especially those with refractory disease, fresh hope by supporting the use of low-dose rituximab as a therapy option for these difficult circumstances.

INTRODUCTION

Pemphigus and pemphigoid represent two major categories of autoimmune blistering skin diseases, each characterized by autoantibodies targeting distinct proteins essential for the structural integrity of the skin.[1,2] Pemphigus is primarily associated with autoantibodies against desmosomal proteins (e.g., desmoglein 1 and 3), leading to intraepidermal blistering.[3] On the other hand, pemphigoid diseases are characterized by autoantibodies targeting hemidesmosomal proteins (e.g., BP180 and BP230), resulting in subepidermal blistering.[4] These autoantibodies disrupt cellular adhesion, causing blister formation, erosion, and significant morbidity.[5] The chronic nature of these diseases and their resistance to conventional therapies

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underscore the need for more effective and targeted treatments.[6]

Mechanism of Action of Rituximab

Rituximab's therapeutic effect is attributed to its specific targeting of CD20, a surface antigen expressed on B cells. By depleting B cells, Rituximab reduces the production of pathogenic autoantibodies, thereby diminishing the autoimmune attack on the skin's structural proteins.[7,8] This mechanism of action is particularly relevant in autoimmune blistering diseases, where the reduction of autoantibody levels is directly correlated with clinical improvement.[9] The versatility of Rituximab, demonstrated across various autoimmune diseases, highlights its potential as a targeted therapy for pemphigus and pemphigoid.[10]

Rationale for Low-Dose Rituximab

The exploration of low-dose Rituximab regimens is driven by several factors. Firstly, the observation that even low doses can achieve significant B-cell depletion suggests that lower doses may suffice for clinical efficacy in non-malignant conditions like pemphigus and pemphigoid. Additionally, lower doses may mitigate the risk of adverse effects commonly associated with Rituximab therapy, such as infusion reactions, infections, and cytopenias. This approach aligns with the principle of using the minimum effective dose to achieve therapeutic goals, potentially broadening the accessibility of Rituximab treatment by reducing costs and enhancing safety profiles.

Against this backdrop, the current study aims to assess the clinical efficacy and safety of low-dose Rituximab in treating autoimmune bullous disorders, with a particular focus on cases refractory to conventional treatments. By evaluating outcomes such as remission rates, durability of response, and incidence of adverse effects, the study seeks to contribute valuable insights into the optimization of Rituximab therapy for these challenging dermatological conditions. Through rigorous investigation, this research endeavors to refine the therapeutic strategies available for pemphigus and pemphigoid, ultimately improving patient outcomes and quality of life.

MATERIALS AND METHODS

Study Setting and Design: This prospective study was conducted in the Department of Dermatology, Venereology, and Leprosy (DVL) at Andhra Medical College, Visakhapatnam, over a period of one year from January 2023 to December 2023. Following informed consent, 20 patients were enrolled to receive two doses of Rituximab (500 mg) at two-week intervals. The intervention was added to the existing treatment regimen for 14 patients and served as the first-line treatment for 6 patients.

Inclusion Criteria

Eligible participants met at least one of the following criteria

Recalcitrant Pemphigus: Patients unresponsive to conventional treatments, marked by new lesions or expansion of existing lesions, despite treatment with prednisolone (1–1.5 mg/kg/day), cyclophosphamide (1–2 mg/kg/day), azathioprine (1–2 mg/kg/day), or dexamethasone-cyclophosphamide pulses.

Steroid Dependence: Patients on continuous prednisone treatment (30–40 mg/day) for over a year, where dose reduction resulted in new lesions.

Contraindications to Standard Therapy: Patients unable to receive conventional treatments due to specific contraindications.

Exclusion Criteria

Patients were excluded if they were pregnant, lactating, had immunodeficiency, active hepatitis, or cardiac disease.

Diagnosis

The diagnosis of pemphigus or pemphigoid was established through clinical evaluation, histopathology, and direct immunofluorescence.

Pretreatment Evaluation

A comprehensive pretreatment assessment was performed, including complete blood count, fasting and postprandial glucose levels, liver and renal function tests, chest X-ray, Mantoux test, electrocardiogram, and screenings for HIV-1, HIV-2, Hepatitis B, and Hepatitis C.

Treatment Protocol

Before Rituximab infusion, patients received premedication with intravenous hydrocortisone (100 mg), pheniramine maleate (8 mg), paracetamol (1 g), and oral Benadryl (10 ml) 30 minutes in advance. Rituximab (500 mg) was infused in 250 ml of normal saline over 4 hours, with a second dose following two weeks later. Vital signs were monitored every 15 minutes during infusion to detect any infusion-related side effects, including fever, chills, headache, rashes, and hypotension.

Monitoring and Follow-up

Treatment responses were quantified using the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) for pemphigus and the Bullous Pemphigoid Disease Area Index (BPDAI) for bullous pemphigoid. Follow-up visits occurred every two weeks for the first three months post-second infusion, then monthly for up to one year.

Endpoints and Outcome Measures

Endpoints included

Disease Activity Control: Time from baseline to cessation of new lesion development and commencement of healing in existing lesions.

Complete Remission on Therapy: No new or existing lesions for at least two months while on minimal therapy.

Complete Remission off Therapy: Absence of new and/or existing lesions for at least two months without any systemic therapy.

Partial Remission: New transient lesions healing within one week, persisting for at least two months,

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with the patient either off all therapy or on minimal therapy.

Ethical Considerations

The study was conducted in accordance with ethical guidelines and standards. Informed consent was obtained from all participants. The study protocol was reviewed and necessary prior permissions taken from concerned authorities.

RESULTS

In this prospective study, we evaluated the efficacy and safety of Rituximab in the treatment of autoimmune bullous diseases, including Pemphigus Vulgaris, Pemphigus Foliaceous, and Bullous Pemphigoid. The study cohort comprised 20 patients, evenly split between genders, with a mean age of 53 years for pemphigus patients and 64 years for pemphigoid patients.

Patient Demographics and Disease Characteristics

The distribution of diagnoses among the patients was as follows: 9 patients had Pemphigus Vulgaris, 3 had Pemphigus Foliaceous, and 8 had Bullous Pemphigoid. The gender distribution across the diseases was nearly balanced, with a slight female predominance in Pemphigus Vulgaris and Foliaceous cases. [Table 1]

Treatment Outcomes

Following the administration of Rituximab, a significant proportion of patients achieved disease remission. Specifically, 58% of pemphigus patients (combining Vulgaris and Foliaceous) achieved complete remission (CR), while 42% showed partial remission (PR). Among bullous pemphigoid patients, 62% achieved CR, and 38% remained in PR. [Table 2]

Long-term Disease Control

During the follow-up period extending from 6 to 12 months, one pemphigus patient progressed from PR to CR, resulting in a total of 66% of pemphigus patients in CR. For bullous pemphigoid, two additional patients achieved CR, elevating the total to 87% in CR. The remaining patients continued to experience PR but required minimal therapy to manage their conditions. [Table 3]

Post-Treatment Status

At the 12-month follow-up, a substantial number of patients were able to discontinue treatment while maintaining remission. Specifically, 8 out of 12 pemphigus patients and 7 out of 8 bullous pemphigoid patients were off all treatment. [Table 4]

Pre and Post-Treatment Disease Severity Scores

Significant improvements were observed in disease severity scores from baseline to the 12-month follow-up. The mean Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) for pemphigus patients decreased from 67.5 to 2.5, and the mean Bullous Pemphigoid Disease Area Index (BPDAI) for pemphigoid patients decreased from 66.6 to 3. [Table 5]

Safety Profile

The treatment was generally well-tolerated. Adverse effects were minimal and included one case of chills and hypotension following infusion, two instances of flu-like symptoms, and one case of herpes zoster during the follow-up period. [Table 6]

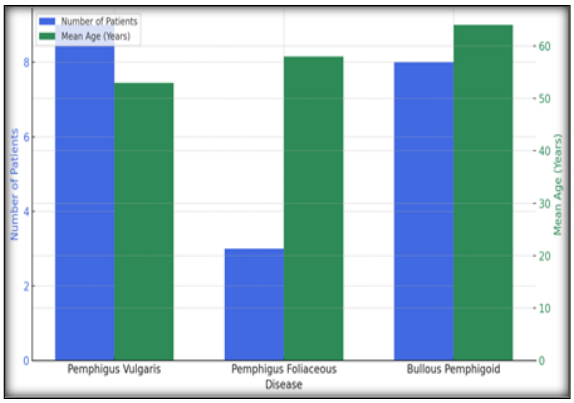

Figure 1: Patient Demographics and Disease Characteristics

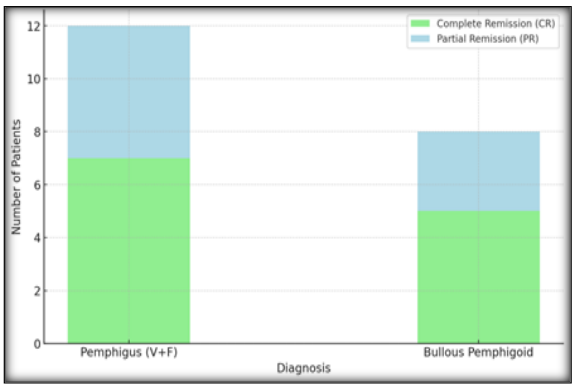

Figure 2: Treatment Outcomes After Rituximab Infusion

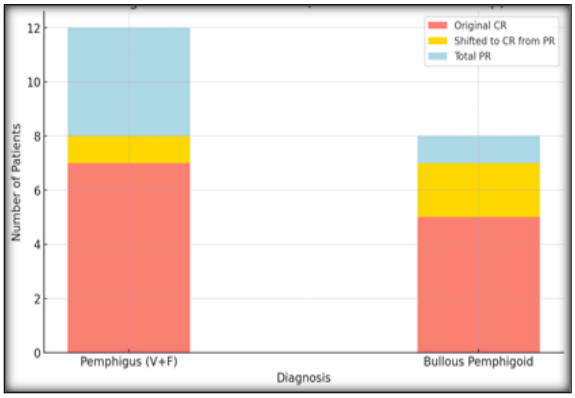

Figure 3: Long term Disease Control (6 to 12 Months Follow-up)

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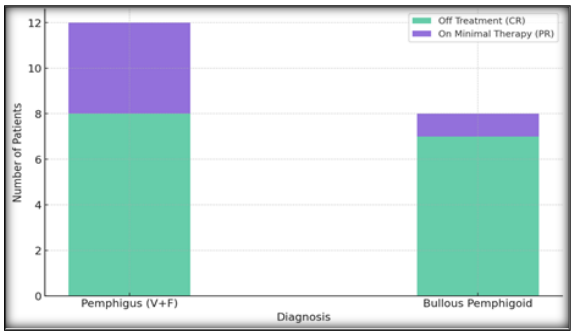

Figure 4: Post -Treatment Status After 12 Months

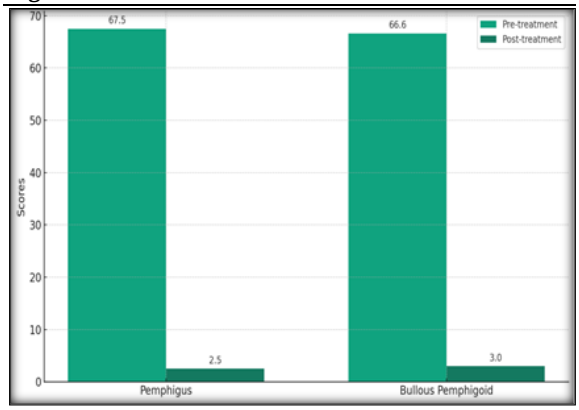

Figure 5: Pre and Post-Treatment Scores by Diagnosis

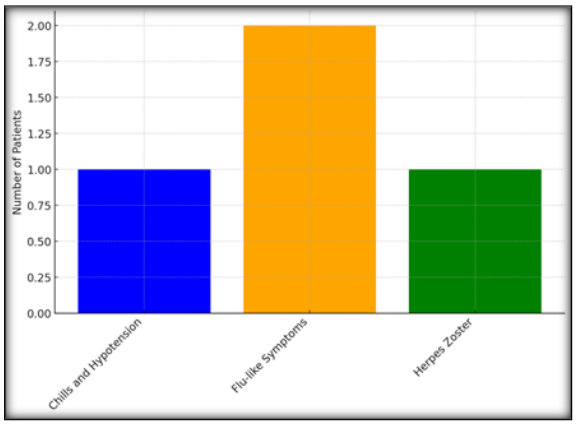

Figure 6: Adverse Effects Observed

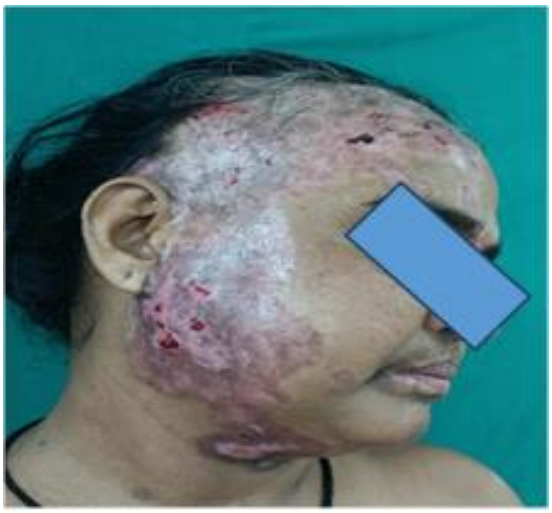

Figure 1: Image of a patient before receiving rituximab and 3 months after 2nd infusion

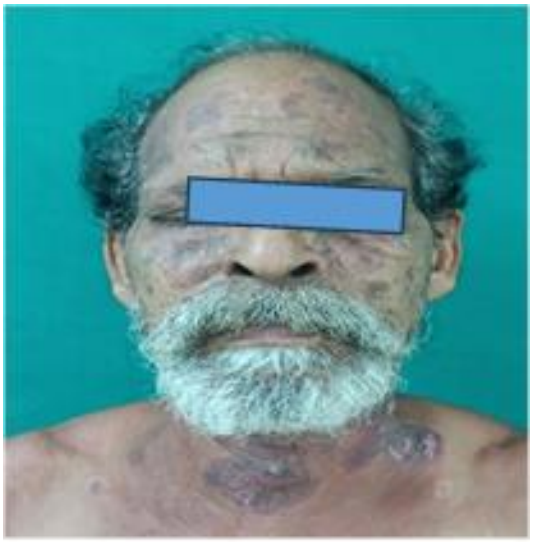

Figure 2: Image of a patient before receiving rituximab and 3 months after 2nd infusion

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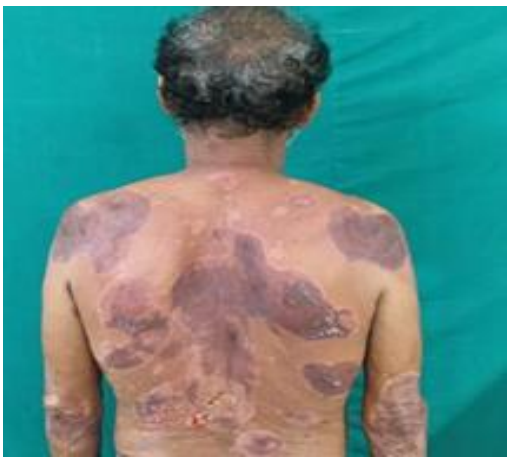


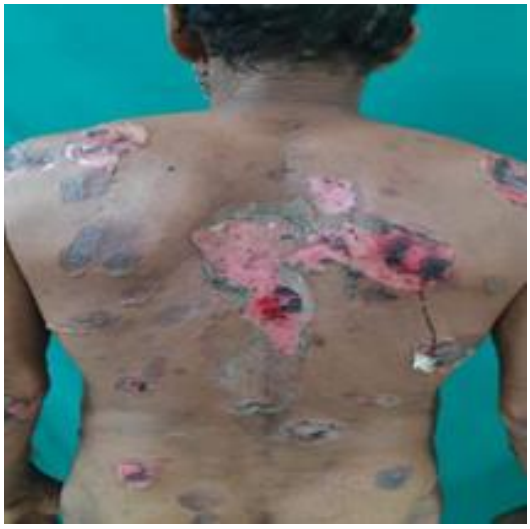
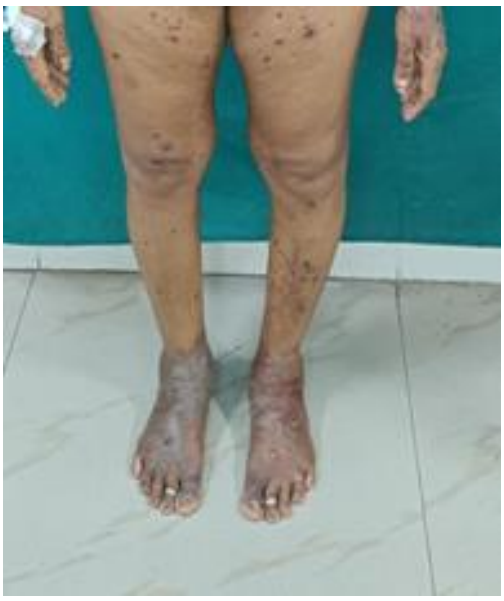


Figure 3: Image of a patient before receiving rituximab and 3 months after 2nd infusion



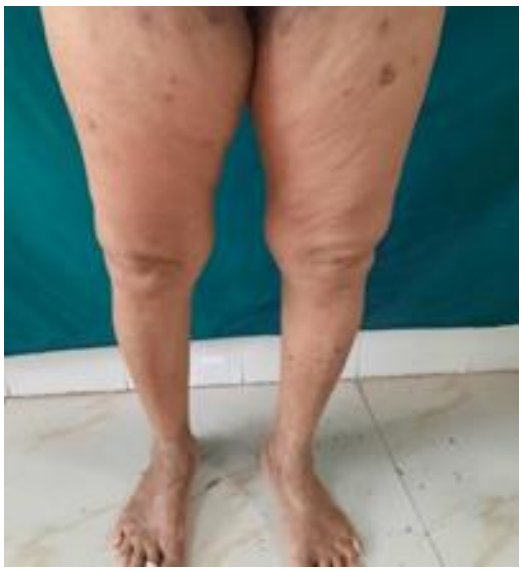


Figure 4: Patient before receiving rituximab and 3 months after 2nd Infusion

Table 1: Patient Demographics and Disease Characteristics

Diagnosis	Number of Patients	Gender Distribution (F/M)	Mean Age (Years)
Pemphigus Vulgaris	9	5/4	53
Pemphigus Foliaceous	3	2/1	58
Bullous Pemphigoid	8	3/5	64

Table 2: Treatment Outcomes After Rituximab Infusion

Diagnosis	Complete Remission (CR)	Partial Remission (PR)	Total Patients
Pemphigus (Vulgaris + Foliaceous)	7 (58%)	5 (42%)	12
Bullous Pemphigoid	5 (62%)	3 (38%)	8

Table 3: Long-term Disease Control (6 to 12 Months Follow-up)

Diagnosis	Shifted to CR from PR	Total CR	Total PR	Total Patients
Pemphigus (Vulgaris + Foliaceous)	1	8 (66%)	4 (34%)	12
Bullous Pemphigoid	2	7 (87%)	1 (13%)	8

Table 4: Post-Treatment Status After 12 Months

Diagnosis	Off Treatment (CR)	On Minimal Therapy (PR)	Total Patients
Pemphigus (Vulgaris + Foliaceous)	8	4	12
Bullous Pemphigoid	7	1	8

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Table 5: Pre and Post-Treatment Scores

Diagnosis	Pre-treatment Score (Mean)	Post-treatment Score (Mean)	Score Type
Pemphigus	67.5 (Range 54-80)	2.5 (Range 0-3)	ABSIS
Bullous Pemphigoid	66.6 (Range 58-75)	3 (Range 0-3)	BPDAI

Table 6: Adverse Effects Observed

Adverse Effect	Number of Patients	Notes
Chills and Hypotension	1	Following infusion
Flu-like Symptoms	2	During follow-up
Herpes Zoster	1	During follow-up

DISCUSSION

our study introduces an important perspective on the use of low-dose rituximab (500 mg, two doses two weeks apart) in the treatment of autoimmune blistering diseases, notably pemphigus and bullous pemphigoid. When comparing the outcomes of our study to those reported by Zakka et al,[15] who utilized the lymphoma and rheumatoid arthritis protocols, our study's results (66% complete remission in pemphigus patients) seem to align more closely with those achieved under the rheumatoid arthritis protocol, despite the lower dosage. This suggests a potential for dose reduction without significantly compromising efficacy, especially in pemphigus.[11,12]

The comparison with Horváth et al.[13] and Polansky et al,[16] further supports the efficacy of low-dose rituximab, indicating that even at reduced doses, a substantial proportion of patients can achieve complete or partial remission.[14] The remarkable similarity between our study's outcomes in bullous pemphigoid patients and those reported by Kremer et al,[17] underlines the potential of low-dose rituximab in offering an effective therapeutic alternative.

Efficacy in Refractory Cases

The success of low-dose rituximab in patients resistant to conventional treatments is noteworthy. This highlights the drug's potential as a valuable option for refractory cases, where other treatments have failed.[18] The fact that a significant proportion of these patients achieved complete remission underscores the need for further research into the mechanisms behind rituximab's efficacy at lower doses.

Safety and Reduction in Concomitant Therapy

The minimal complications reported in our study, alongside major clinical improvements and a decreased need for steroids and other immunosuppressants, point to the benefits of low-dose rituximab beyond its efficacy. The reduction in the daily dosage of concomitant therapies could lead to fewer side effects and a better quality of life for patients, an aspect that is of paramount importance in chronic diseases.

Limitations and Future Directions

While our study presents compelling evidence for the use of low-dose rituximab, it is important to consider limitations such as the small sample size and the need for longer follow-up to fully understand the durability of remission. Future research should aim to include larger cohorts, longer follow-up periods, and a comparison between different dosing regimens in a randomized controlled setting. Additionally, investigating the pharmacokinetics and pharmacodynamics of rituximab in this context could provide deeper insights into how the drug works at lower doses and how treatment can be further optimized.

CONCLUSION

Our study highlights the potential of low-dose Rituximab as an effective and well-tolerated treatment option for autoimmune bullous disorders. The observed rates of disease control, remission, and favorable safety profile support its consideration as a valuable therapeutic strategy, particularly in cases resistant to conventional therapies. Further research is needed to confirm these findings and optimize treatment protocols for optimal patient outcomes. Through continued investigation and clinical experience, Rituximab may emerge as a cornerstone in the management of autoimmune bullous disorders, offering hope for improved quality of life and long-term disease control for affected individuals.

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