

## Evaluating the Effectiveness and Safety of Low-Dose Rituximab for Immunobullous Disorders

Bhuvnesh Shah<sup>1</sup>, Keya B Shah<sup>2</sup>, Girish H Shah<sup>3</sup>

<sup>1</sup>Associate Professor and Head, Department of Dermatology, Kiran medical College, Surat, Gujarat, India

<sup>2</sup>Consultant, Skin Care Institute, Surat, Gujarat, India

<sup>3</sup>Senior Consultant, Skin Care Institute, Surat, Gujarat, India

Received: 01-07-2024 Revised: 15-08-2024 / Accepted: 21-09-2024

Corresponding author: Dr. Keya B Shah

Conflict of interest: Nil

### Abstract

**Background and Aim:** Immunobullous diseases represent a unique category of autoimmune blistering conditions characterized by the presence of lesions that can occur both within the epidermis and beneath it. This research aimed to assess the effectiveness of low-dose rituximab in treating immunobullous diseases, while also prioritizing its safety for patients.

**Material and Methods:** The study included a total of 40 patients. A diagnosis of pemphigus was established through clinical evaluation, histopathological examination, and direct immunofluorescence testing. The Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) for pemphigus was used to measure the frequency of treatment responses during monitoring and follow-up phases.

**Results:** This study included a total of forty patients, consisting of 25 males and 15 females who participated in the research. An analysis of Disease Severity Scores was conducted before and after treatment. Between the initial assessment and the follow-up after one year, there was a significant increase in disease severity as reflected in the scores. Individuals diagnosed with pemphigus experienced a significant decrease in the mean Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), dropping from 62.2 to 2.1.

**Conclusion:** The low-dose regimen showed similar short-term effectiveness and response duration, while also being relatively safer and more cost-effective.

**Keywords:** Autoimmune Bullous Skin Disorder Intensity Score, Bullous Pemphigoid, Immunobullous Diseases, Rituximab.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

### Introduction

Pemphigus is a chronic autoimmune blistering disorder that affects the skin and mucous membranes. It has two main variants: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is the most prevalent subtype, accounting for 75 to 92% of all pemphigus cases. It is caused by autoantibodies that target desmogleins, which are proteins found on the surface of cells. Historically, pemphigus was associated with high mortality and morbidity; however, the introduction of corticosteroids significantly improved the prognosis of this previously fatal disease, reducing the mortality rate to less than 10%. [1]

A significant advancement in the treatment of pemphigus came with the use of rituximab (RTX), introduced by Heizmann et al. Rituximab is a chimeric monoclonal anti-CD20 antibody that targets B lymphocytes, leading to cell death through Fc-mediated lysis. It is utilized in cancer

therapy and was initially approved for lymphoma due to its considerable effectiveness in reducing both normal and malignant B-cells. [1,2] In most studies, the therapeutic protocol for RTX has shown similarities to that used for B cell lymphoma. This protocol includes an initial treatment phase with either four weekly doses of 375 mg/m<sup>2</sup> or two doses of 1,000 mg administered on days 1 and 15, followed by reinfusion every six months. [3,4]

Bullous Pemphigoid, Pemphigus Vulgaris, and Pemphigus Foliaceus are the three most prevalent forms of immunobullous diseases. Immunobullous diseases represent a unique category of autoimmune blistering conditions characterized by the presence of lesions that can occur both within the epidermis and beneath it. The occurrence of these diseases is reported to differ from one country to another. In Germany, the incidence rate is 0.5

cases per million inhabitants, whereas in India, it stands at 4.4 cases per million population annually. In Saudi Arabia, the incidence is 50 cases for every million inhabitants. [5,6] The investigation of low-dose Rituximab prescription Regime is influenced by several important factors. Research indicates that even low doses can lead to considerable B-cell depletion. This finding serves as initial evidence that reduced doses might be adequate for effective clinical outcomes in treating non-malignant conditions like pemphigus and pemphigoid cancer. Furthermore, utilizing lower doses may decrease the chances of encountering adverse effects commonly linked to Rituximab therapy. Potential concerns may encompass infusion reactions, infections, and cytopenias.[7,8] This research aimed to assess the effectiveness of low-dose rituximab in treating immunobullous diseases, while also prioritizing its safety for patients.

### Materials and Method

Present cross-sectional; study was conducted at the Department of Dermatology, Tertiary Care Teaching Institute of India for the duration of 1 year. The study involved a total of forty patients. Before participating, patients received comprehensive information about the research project and were required to sign a consent form.

The new medication has been integrated into the existing treatment plan for 28 patients, serving as the primary treatment for 12 of those individuals. The study revealed that the average age of the patients included was 50 years. The following criteria were established to identify participants for inclusion in the study:

The study included individuals who did not experience improvement with standard therapies, as evidenced by the appearance of new lesions or the enlargement of existing ones, despite receiving available medications. It also involved individuals who were unable to undergo standard treatments due to specific contraindications. Additionally, participants who had been on continuous prednisone therapy (30–40 mg/day) for more than a year and developed new lesions after a dose reduction and individuals with desmoglein antibody (anti-desmoglein-1 and/or anti-desmoglein-3) levels >20 were included in the study.

Pregnant and breastfeeding women, immunodeficient cases, cases with active hepatitis and cardiac disease were excluded from study.

The age of the patient, gender, duration of disease and a detailed history were recorded. A clinical evaluation, histopathology, and direct immunofluorescence were employed to establish a diagnosis of pemphigus. A comprehensive pre-treatment evaluation was conducted. Thirty minutes

prior to the procedure, patients received premedication that included 100 mg intravenous methylprednisolone and 500 mg of paracetamol per orally, 30 min before the infusion. Every patient should preferably be admitted and /intensive care unit/ward with facilities for close monitoring by a qualified medical practitioner. Patients received pre-hydration with an infusion of 500 ml of 0.9% sodium chloride solution.

Pre-treatment workup included a complete hemogram, Liver function tests, renal function tests, fasting and postprandial blood sugar levels, chest X-ray, electrocardiogram, Mantoux test, screening for viral infections including Hepatitis B, Hepatitis C, HIV and VDRL test.

**Dosing and Interval:** Administer 1 gram Injection rituximab on days 1 and 14, followed by 500 mg at month 12, and then every 6 months thereafter, or as indicated by clinical evaluation.

**Preparation of the Infusion:** Two vials will provide 1 g in 100 ml. Mix this with 400 ml of normal saline after discarding 100 ml from a 500 ml bottle.

**Infusion Rate:** The total volume to be infused is 500 ml. The first infusion should commence at a rate of 50 mg/h. If no infusion toxicity is observed, the rate can be increased by 50 mg/h every 30 minutes, up to a maximum of 400 mg/h.

### Infusion schedule:

30 ml/h for the first 30 minutes (15 ml)

60 ml/h for the next 30 minutes (30 ml)

90 ml/h until infusion is complete (455 ml over 5 hours)

The total duration for the first infusion is 6 hours.

**Patient Monitoring During Infusion:** Monitor pulse, blood pressure, respiratory rate, and perform pulse oximetry every 30 minutes. Observe for any infusion reactions such as fever, rigors, nausea, vomiting, headache, or hypotension. Most infusion reactions can be managed by reducing the infusion speed. However, serious adverse effects like angioedema and anaphylaxis necessitate the immediate cessation of the infusion.

The Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) for pemphigus was used to measure the frequency of treatment responses during monitoring and follow-up phases. The patient is advised to have a complete hemogram done every three months.

### Results

This investigation focused on examining the efficacy and safety of Rituximab as a treatment option for autoimmune diseases, specifically

Pemphigus Vulgaris. This study involved a total of forty patients, comprising 25 males and 15 females who took part in the research. The study indicated a preference for male participants. Understanding the potential complications associated with treatment is crucial for informed decision-making. It is important to be aware of the risks involved and to discuss them with your healthcare provider to ensure the best possible outcomes. After receiving Rituximab, a significant number of patients experienced remission of their condition. The Condition after Treatment Over the twelve-month

follow-up period, many patients successfully discontinued their treatment while maintaining remission. Analysis of Disease Severity Scores Prior to and Following Treatment Between the initial assessment and the follow-up after a year, there was a significant increase in the severity of the disease based on the scores. Individuals diagnosed with pemphigus showed a significant reduction in the mean Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), decreasing from 62.2 to 2.1.

**Table 1: Pre and Post-Treatment Autoimmune Bullous Skin Disorder Intensity Scores**

Diagnosis	Pre treatment score	Post treatment score
Pemphigus	62.2	2.1

**Table 2: Patient Demographics and Disease Characteristics**

Diagnosis	Number of patients	Gender distribution
Pemphigus vulgaris	40	25 males 15 females

### Discussion

Rituximab shows promise as a safe and effective option for treating immunobullous diseases in Nepalese patients, although it's important to note that the evaluation of its effectiveness involved a limited number of patients. The clinical response was noted to be favourable in all of these patients, reflecting both the early management of the disease and a decrease in the overall duration of steroid use. During the short-term follow-up period, no patients were reported to have experienced any adverse effects. Research indicates that both low-dose and standard-dose RTX are effective treatments for MG, with low-dose RTX showing greater efficacy. [9]

Low-dose rituximab demonstrates significant clinical application value due to its safety and effectiveness, along with a favourable cost-effectiveness ratio. Determining the appropriate patients for low-dose rituximab during the clinical period remains a challenge, as does identifying the most effective combination therapy for this treatment. The American Society of Haematology (ASH) guideline panel recommends rituximab for patients who have had their disease for less than one year and prefer to avoid surgery or long-term medication. Administering rituximab earlier may lead to improved long-term response rates. [10]

The findings from Horváth et al. and Polansky et al. further support the effectiveness of low-dose rituximab. This shows that even with lower doses, many patients can attain either complete or partial remission from their cancer. [11] To fully grasp the factors influencing the duration of remission, it is important to acknowledge certain limitations, including the small sample size and the need for an

extended follow-up period. Future research should aim to include larger groups of participants, extend follow-up durations, and compare different dosing regimens within the framework of a randomised controlled trial.

### Conclusion

The findings suggest that the low-dose rituximab regimen may be a promising alternative to the standard-dosage regimen, especially in contexts where resources are constrained. The low-dose regimen showed similar short-term effectiveness and response duration, while also being relatively safer and more cost-effective.

Ongoing research and clinical experience suggest that Rituximab may play a vital role in the treatment of bullous disorders. This would offer individuals impacted by the condition the chance to improve their quality of life and achieve sustained disease management.

### References

1. Doubek M, Šmída M. Treatment of chronic lymphocytic leukemia with monoclonal antibodies, where are we heading? Expert Review of Hematology. 2015;8(6):743-764.
2. Heizmann M, Itin P, Wernli M, Borradori L, Bargetzi MJ. Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: Report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. Am J Hematol. 2001;66:142-4.
3. Coutinho R, Flook M, Pria A, et al. Non-Hodgkin Lymphoma-Clinical. Paper presented at: 18th Congress Of The European Hematology Association Stockholm, Sweden June 13-16, 20132008.

4. Cao H, Ma X. Rituximab in the Treatment of Non-Infectious Uveitis: A Review. *Journal of Inflammation Research*. 2024;6765-6780.
5. Wilken R, Patel FB, Sultani H, et al. Pathophysiology of autoimmune bullous diseases: Nature versus nurture. *Indian Journal of Dermatology*. 2017;62(3):262-267.
6. Schmidt E, Zillikens D. Modern diagnosis of autoimmune blistering skin diseases. *Autoimmunity reviews*. 2010;10(2):84-89.
7. Kim S-H, Kim W, Li XF, Jung I-J, Kim HJ. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. *Archives of neurology*. 2011;68(11):1412-1420.
8. Choi K, Hong Y-H, Ahn S-H, et al. Repeated low-dose rituximab treatment based on the assessment of circulating B cells in patients with refractory myasthenia gravis. *Therapeutic Advances in Neurological Disorders*. 2019;12: 1756286419871187.
9. Chen D, Oduyungbo A, Csinady E, et al. Rituximab is an effective treatment in patients with pemphigus vulgaris and demonstrates a steroid-sparing effect. *British Journal of Dermatology*. 2020;182(5):1111-1119.
10. Chandramohan P, Jain A, Antony G, Krishnan N, Shenoy P. Low-dose rituximab protocol in rheumatoid arthritis—outcome and economic impact. *Rheumatology advances in practice*. 2021;5(1):rkaa077.
11. Cao P, Xu W, Zhang L. Rituximab, omalizumab, and dupilumab treatment outcomes in bullous pemphigoid: a systematic review. *Frontiers in Immunology*. 2022;13: 928621.