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REAL-WORLD EFFECTIVENESS AND SAFETY OF RITUXIMAB IN MODERATE-TO-SEVERE PEMPHIGUS VULGARIS: A PROSPECTIVE COHORT STUDY OF 61 IRAQI PATIENTS

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Abstract:

Background: Pemphigus vulgaris (PV) is a chronic and potentially life-threatening autoimmune blistering disease characterized by intraepidermal acantholysis, and its prevalence is relatively high among the Iraqi population. Rituximab, an anti-CD20 monoclonal antibody, is currently recommended as the first-line therapy for moderate-to-severe PV; however, its use in Iraq remains limited.
Objective: To evaluate the clinical efficacy and safety of rituximab in patients with moderate-to-severe PV.
Methods: This prospective cohort study included 61 patients with moderate-to-severe PV at Morjan Teaching Hospital between January 2022 and December 2024. Rituximab was administered as four intravenous infusions of 500 mg at 2-week intervals. The primary outcome was complete remission off systemic therapy at 12 months. Secondary outcomes included relapse-free survival over 36 months, cumulative corticosteroid exposure, adverse events, and changes in antidesmoglein 1 and 3 autoantibody titers. Clinical activity, serological markers, and quality of life were assessed at predefined intervals.
Results: Complete remission off therapy at 12 months was achieved in 39 patients (63.9%). The median relapse-free survival was 19 months, and 47.5% of patients remained in remission at 36 months. Antidesmoglein 1 and 3 antibody levels were significantly reduced ($p < 0.001$). No serious adverse events or deaths were reported. Mild infusion-related reactions occurred in 11.5% of the patients. The 3-year cumulative corticosteroid dose was significantly reduced, confirming a steroid-sparing effect.
Conclusions: Rituximab demonstrated high efficacy and a favorable safety profile in Iraqi patients with moderate-to-severe PV, including those with refractory disease. Although high rates of short-term remission were achieved, long-term relapse remains a concern, highlighting the need for maintenance strategies to optimize sustained disease control.

Keywords: Pemphigus vulgaris; Rituximab; Autoimmune blistering diseases; Corticosteroid-sparing effect; Biologics; Iraq.

INTRODUCTION

Pemphigus vulgaris (PV) is an uncommon but potentially life-threatening immunological blistering illness associated with the flow of autoantibodies against desmogleins (Dsg), which are critical adhesion proteins in the epidermis. The condition is characterized by intraepidermal blistering of the skin and mucous membranes, primarily involving the oral cavity and trunk, secondary to acantholysis [1,2]. PV is the most common and severe disease of the pemphigus spectrum, which encompasses the less well-known subtypes such as pemphigus foliaceus, paraneoplastic pemphigus, and immunoglobulin A pemphigus [3]. PV has an autoimmune pathophysiology involving autoantibodies against Dsg 3 (mucosal involvement) and Dsg 1 (cutaneous involvement), with clinical manifestations varying according to the specific target antigen [4]. For instance, pemphigus foliaceus, a form of pemphigus associated exclusively with Dsg 1 autoantibodies, typically presents with superficial erosion confined to seborrheic areas without mucosal involvement [5].
Epidemiologically, PV shows marked geographical variation, being most prevalent in the Middle East, parts of Latin America, and South Asia [2,6]. In Iraq, PV shows particularly high incidence rates in the

central and southern provinces [7]. This distribution may be attributed to genetic factors, and evidence from Iraqi populations has indicated a possible association between PV and ST18 gene polymorphisms [8].

Systemic corticosteroids and systemic immunosuppressants (i.e., azathioprine or mycophenolate mofetil) have been used as conventional therapeutic agents for PV. However, despite their efficacy in reducing disease activity, these regimens are associated with substantial chronic toxicity, increased relapse risk, infections, and metabolic syndrome [3,9]. An effective alternative has emerged in the form of biologic therapies. Rituximab, a chimeric monoclonal antibody directed against C20-positive B cells, has demonstrated enhanced relapse rates and the ability to reduce steroid-sparing effects [10]. Nevertheless, low-resource settings, such as Iraq, continue to have limited access to these therapies due to financial, regulatory, and logistical constraints [11,12].

This study examined the clinical outcomes of rituximab therapy in patients with moderate-to-severe PV in central Iraq. The primary outcome was the rate of complete remission off therapy 1 year after treatment. Secondary outcomes included assessment of the safety profile, corticosteroid exposure, and 3-year relapse-free survival as well as identification of practical barriers to rituximab administration in a resource-limited setting.

METHODS AND MATERIAL

Study Design and Population

This single-center prospective cohort study was conducted at the Department of Dermatology at Morjan Teaching Hospital in Iraq. From January 2022 to December 2024, 61 patients with moderate-to-severe PV who met the eligibility criteria were enrolled. All patients received rituximab induction therapy as four doses of 500 mg intravenous infusions administered 2 weeks apart.

Patients underwent comprehensive clinical assessments at baseline before rituximab administration, followed by scheduled follow-up visits at 3, 6, 12, 18, 24, and 36 months after treatment. The primary outcome was complete clinical remission off systemic therapy at 1 year after treatment. Secondary outcomes included relapse rate, relapse-free survival, remission duration, adverse events, and serological response over the 3-year follow-up period. Serum anti-Dsg 1 and 3 autoantibody levels were assessed during all study visits.

Setting

Morjan Teaching Hospital is a major public tertiary care center affiliated with Babylon Medical College. The Department of Dermatology includes inpatient wards and outpatient clinics staffed by board-certified dermatologists, residents, and nurses. Approximately 200–250 patients are seen weekly in outpatient clinics, including those with autoimmune blistering diseases such as PV. The 30-bed inpatient dermatology service admits approximately 8–12 patients with PV monthly for disease management when outpatient treatment fails. Participants were recruited from both outpatient and inpatient settings. After enrollment and initial rituximab infusions, all subsequent follow-ups were conducted during routine outpatient dermatology visits over 3 years.

Sampling

A nonprobability, consecutive sampling method was used to enroll eligible patients with PV until the predetermined sample size was reached. The sampling frame included all moderate-to-severe, biopsy-confirmed patients with PV presenting to the Department of Dermatology of the hospital. Key eligibility criteria included mucocutaneous involvement, high-dose corticosteroid dependence, and no prior exposure to rituximab or other biologic therapies. Eligible patients were approached consecutively for recruitment and were invited to provide written informed consent. Assuming 80% power to detect a 30% difference in the 1-year remission rate compared with 40% under conventional therapy ($\alpha = 0.05$), the target sample size was 61 after accounting for a 10% dropout rate.

Data Collection

Baseline demographic and clinical data were collected at enrollment, including PV history, prior treatments, comorbidities, and physical examination findings. Cutaneous involvement was documented using medical photography. Blood samples were collected for safety laboratory tests and antibody assays.

During follow-up visits, complete skin and mucosal examinations were performed to assess disease activity according to published criteria, categorizing cases as complete remission, partial remission, active disease, or relapse. Adverse events, concomitant medication use, and healthcare utilization were recorded. Serial antibody levels were also measured.

Assessments and Instruments

Physical examination findings were documented using standard dermatological terminology. Disease severity was classified using Harman's criteria based on body surface area involvement as mild (<10%), moderate (10%–30%), or severe (>30%). The following standardized definitions were used to categorize disease activity:

Complete remission: no lesions while off therapy for ≥2 months
Partial remission: new transient lesions that heal spontaneously
Active disease: presence of new lesions or failure of existing lesions to heal
Relapse: ≥3 new nonhealing lesions per month

Commercially available enzyme-linked immunosorbent assay kits were used to quantify serum anti-Dsg 1 and 3 antibody levels, classified as negative (<20 U/mL), borderline positive (20–100 U/mL), or strongly positive (>100 U/mL).

Analysis

Descriptive statistics were used to summarize patient characteristics and outcomes. The primary endpoint was the proportion of patients who achieved complete remission at 1 year. Kaplan–Meier analysis was used to estimate relapse-free survival. Changes in antibody titers were assessed using the Wilcoxon signed-rank test. SPSS software was used for all statistical analyses.

Ethical Approval

The research protocol was approved by the institutional ethics committee (approval no.: ETH-2022-05-12) on January 15, 2024. Informed consent was obtained from all participants, and confidentiality and privacy were maintained throughout the study. The study involved minimal risk, as rituximab is an established therapy for PV. Patient safety was ensured throughout, and the findings are intended to contribute to improved PV management.

RESULTS

Baseline Characteristics

This prospective cohort study enrolled 61 patients diagnosed with moderate-to-severe PV. Table 1 presents their baseline demographic and disease characteristics.

Table 1. Baseline Demographics and Disease Characteristics (N = 61)

Characteristic	Number (%) or mean ± SD
Age (years)	41.7 ± 12.3
Sex	
Male	27 (44.3%)
Female	34 (55.7%)
Disease duration (years)	3 (2–5) (median [IQR])
Disease severity	
Moderate	18 (29.5%)
Severe	43 (70.5%)
Cutaneous lesions	61 (100%)
Oral mucosal lesions	44 (72.1%)

Note: IQR, interquartile range; SD, standard deviation.

At baseline, this cohort comprised Iraqi patients with longstanding, severe, and widespread PV, reflecting those requiring systemic immunosuppression in real-world clinical practice. The demographic profile indicates a representative study population of middle-aged adults with a slight female predominance, as is typical of autoimmune disorders, as shown in Figure 1.

Rituximab Administration
Each patient received rituximab intravenously at a total dose of 500 mg per infusion, administered in four doses at 2-week intervals, following a standardized infusion protocol described in Table 2.

Table 2. Rituximab Infusion Protocol

Infusion number	Initial infusion rate	Infusion rate increase	Maximum infusion rate
First infusion	50 mL/h for 30 min	Increase by 50 mL/h every 30 min	400 mL/h
Second infusion	100 mL/h for 30 min	Increase by 100 mL/h every 30 min	400 mL/h

Note: The infusion protocol was designed to minimize infusion-related reactions by gradual rate escalation.

PRIMARY OUTCOME ANALYSIS

Complete Remission Rate at 1 Year
The primary outcome was the proportion of patients achieving complete clinical remission off all systemic therapy at 1 year following rituximab induction. Complete remission was defined as the absence of new or established lesions for ≥2 months after discontinuation of all PV medications. At the 12-month study visit, 39 of 61 patients (63.9%, 95% confidence interval [CI] 51.2%–75.5%) met the criteria for complete remission, as shown in Table 3.

Table 3. Complete Remission Rates at 1 Year

Remission status	Number of patients (n = 61)
Complete remission	39
Incomplete remission	22
Total	**61**

This demonstrates a high rate of complete remission at 1 year following four doses of rituximab.

Time Course of Complete Remission
The onset and duration of complete remission over the 3-year follow-up period are depicted in Figure 2. At 3 months after rituximab initiation, 39 patients (63.9%) had achieved complete remission. This number peaked at 39 patients (63.9%) at the 12-month visit but subsequently declined to 32 patients (52.5%) at 36 months, illustrating the relapsing–remitting course of PV despite induction therapy with rituximab.

SECONDARY OUTCOME ANALYSIS

Disease Status Over Time
The clinical response to rituximab was evaluated based on disease status at each study visit (i.e., complete remission, partial remission, active disease, or relapse), as summarized in Table 4.

Table 4. Pemphigus Vulgaris Disease Status Over 3 Years of Follow-Up

Time point	Complete remission (n, %)	Partial remission (n, %)	Active disease (n, %)	Relapse (n, %)
3 months	39 (63.9%)	15 (24.6%)	7 (11.5%)	-
6 months	34 (55.7%)	15 (24.6%)	12 (19.7%)	15 (24.6%)
12 months	39 (63.9%)	10 (16.4%)	12 (19.7%)	19 (31.2%)
18 months	29 (47.5%)	12 (19.7%)	20 (32.8%)	23 (37.7%)
24 months	27 (44.3%)	13 (21.3%)	21 (34.4%)	26 (42.6%)
36 months	32 (52.5%)	-	29 (47.5%)	29 (47.5%)

Note: Relapse was defined as the presence of ≥3 new nonhealing lesions per month.
By 12 months, 63.9% of patients achieved complete remission; however, relapse rates increased over time, with 47.5% of patients experiencing relapse by 36 months.

Relapse-Free Survival
The median relapse-free survival was 19 months, as shown in Figure 3. Kaplan–Meier analysis indicated that 100% of patients were relapse-free at 6 months, decreasing steadily to 47.5% at 36 months.

Autoantibody Levels
Rituximab administration resulted in a significant progressive decline in serum autoantibody levels over the 3-year follow-up period (Table 5).

Table 5. Median Serum Autoantibody Levels Before and After Rituximab Therapy

Time point	Median anti-Dsg1 titer (U/mL) (IQR)	Median anti-Dsg3 titer (U/mL) (IQR)
Baseline	182 (105–412)	248 (132–512)
3 months	92 (34–198)	112 (51–256)
6 months	26 (10–76)	38 (14–92)
12 months	14 (5–24)	19 (8–38)
18 months	9 (2–16)	12 (3–26)
24 months	6 (1–12)	8 (2–18)
36 months	4 (0–8)	6 (0–14)

Note: $p < 0.001$ compared with baseline.

SAFETY OUTCOMES

Adverse Events
The risk of adverse events associated with rituximab was low, and most reactions were mild (Table 6). The most frequently observed adverse event was a mild infusion-related reaction (11.5%) with flu-like symptoms. Infections requiring antibiotic treatment occurred in three patients (4.9%), and transient liver function abnormalities were observed in two patients (3.3%). No serious adverse events or treatment-related deaths were reported.

Table 6. Adverse Events Among Study Participants Over 3 Years of Follow-Up

Adverse event	Number of patients (%)
Infusion reactions	7 (11.5%)
Infections	3 (4.9%)
Abnormal liver function tests	2 (3.3%)
Hospitalizations	1 (1.6%)
Major adverse events	0 (0%)
Deaths	0 (0%)

Corticosteroid Exposure
Concomitant use of high-dose corticosteroids was not allowed, although rescue therapy with low-dose corticosteroids was permitted. The median cumulative dose of rescue corticosteroids was 220 mg prednisone-equivalent (IQR 0–345 mg), as shown in Figure 6. A substantial proportion of patients (34.4%) did not require any rescue corticosteroids. Only 9.8% required a cumulative dose of >500 mg, whereas 29.5% received 101–500 mg. This minimal corticosteroid exposure indicates a substantial steroid-sparing effect of rituximab.

DISCUSSION

The results of this study add to the growing evidence supporting the efficacy and safety of rituximab in the treatment of moderate-to-severe PV. The 1-year complete remission rate of 63.9% in this Iraqi cohort is comparable to previously reported rates of 59%–76% from randomized clinical trials and observational studies, with variation depending on dosing regimens and patient selection [13,14].

A previous multicenter randomized trial demonstrated that rituximab was more effective than prednisone monotherapy, resulting in faster and more durable remission [15]. Similar efficacy has been observed in real-world cohorts across different populations, including patients with refractory disease [16,17]. Moreover, our cohort showed a remission duration comparable to global reports. The median relapse-free survival of 19 months is consistent with findings by Perifani et al., who reported similar timelines in a real-world Greek population [17]. Nevertheless, the remission rate declined over 36 months, highlighting the relapsing–remitting course of PV and suggesting the need for maintenance therapy or repeat rituximab infusions to achieve long-term disease control [18,19].

The most notable finding in this study was the gradual decrease in serum anti-Dsg 1 and 3 antibody titers, which was observed in parallel with clinical remission. This finding supports the key role of B-cell depletion in modifying the underlying autoimmune process. The immunological effects of biosimilar rituximab have also been demonstrated in prospective analyses, with similar reductions in antibody activity reported by Toosi et al. [20]. Baseline anti-Dsg 3 levels were associated with relapse, consistent with the findings of previous studies that highlighted the prognostic value of serological markers.

The use of rituximab in this Iraqi cohort was safe. Mild infusion-related reactions were observed in 11.5% of patients, with no life-threatening adverse events or fatalities. These findings are consistent with those of previous meta-analyses and long-term studies of rituximab in autoimmune blistering diseases, which have reported low adverse event rates [21]. However, clinicians must be aware of the rare but severe infections such as Pneumocystis jirovecii pneumonia, particularly in older individuals or otherwise immunosuppressed patients [22]. Notably, rituximab achieved a significant steroid-sparing effect in this population. The mean cumulative corticosteroid dose was significantly lower than that associated with traditional regimens, thereby reducing the risk of steroid-related complications, including osteoporosis, diabetes, and hypertension [23]. Khandelwal et al. reported that rituximab reduces corticosteroid burden and improves the quality of life of patients.

Despite these encouraging results, several systemic barriers to rituximab use remain in Iraq. Widespread access is limited by high acquisition costs, restricted governmental supply of biosimilars, and the absence of a structured biosimilar regulatory pathway. A local case series has described these barriers, noting that delayed treatment often leads to poor disease outcomes. Mohammed et al. outlined similar challenges limiting the use of biologics in cancer care within the Iraqi health system, including structural and policy-related constraints. These issues highlight the need for improved access through strategies such as biosimilar subsidies and inclusion of rituximab in national treatment frameworks.

The epidemiological context of PV in Iraq is also reflected in the findings of this study. Patients typically present with chronic disease characterized by extensive, longstanding mucocutaneous involvement and steroid dependence, likely reflecting delayed diagnosis, limited specialist access, and low public awareness. In addition, recent genetic evidence has implicated ST18 gene polymorphisms in disease susceptibility among Iraqi patients, which may contribute to more severe disease phenotypes in this population [24].

The limitations of this study include its single-center design, relatively small sample size, and the absence of a comparator group. However, the generalizability of the findings is supported by the longitudinal follow-up, real-world clinical setting, and use of standardized outcome measures. Nevertheless, further multicenter studies in low-resource settings such as Iraq are needed to evaluate rituximab dosing strategies, maintenance therapy, and biosimilar efficacy.

CONCLUSION

This Iraqi cohort study substantiates the clinical efficacy of rituximab induction therapy in moderate-to-severe PV. The 1-year complete remission rates, rapid onset of response, and relapse patterns observed in this cohort are consistent with global observational data on rituximab use in PV.

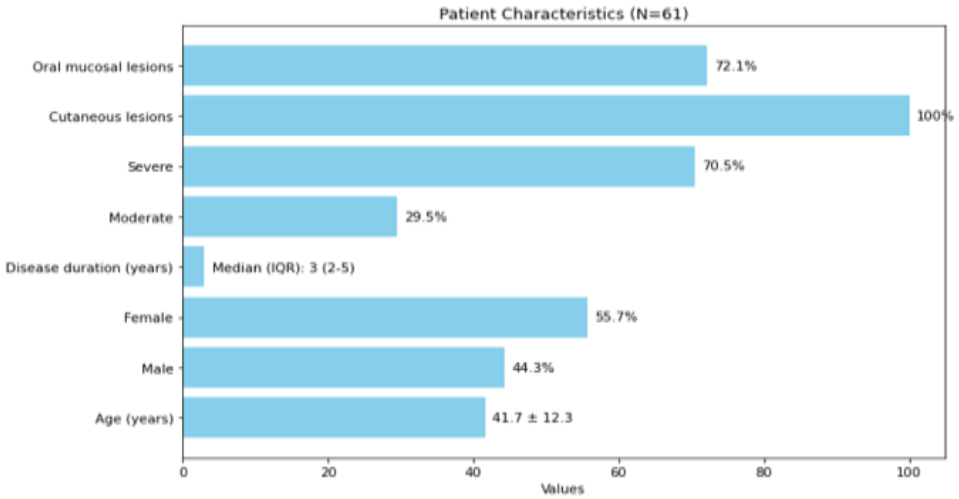
In our cohort, 63.9% of patients achieved complete remission at 12 months following intravenous rituximab therapy (four doses of 500 mg), which is comparable to the reported rates of 67% and 69% in the United States and Italian populations, respectively. A recent meta-analysis of 18 studies reported a pooled 1-year complete remission rate of 67.6% with rituximab. The onset of remission was rapid, with

63.9% of patients achieving complete remission at 3 months after therapy initiation. This may reflect the rapid depletion of pathogenic B cells and subsequent reduction in autoantibody production compared with conventional immunosuppressive regimens that require prolonged administration.
Remission persistence was limited, with a median relapse-free survival of 19 months. At 36 months, less than half of the patients (47.5%) remained in complete remission. This decline in sustained remission is consistent with reported late relapse rates of 30%–50% at 18–36 months in other cohorts. This may be explained by B-cell repopulation and rebound autoantibody production as the effect of rituximab decreases. Potential strategies to prolong remission include fixed-interval retreatment, biomarker-guided redosing, or combination with maintenance immunosuppressive therapy. In conclusion, although single-course induction is highly effective in the short term, further studies are required to optimize long-term treatment strategies.

List of Figures

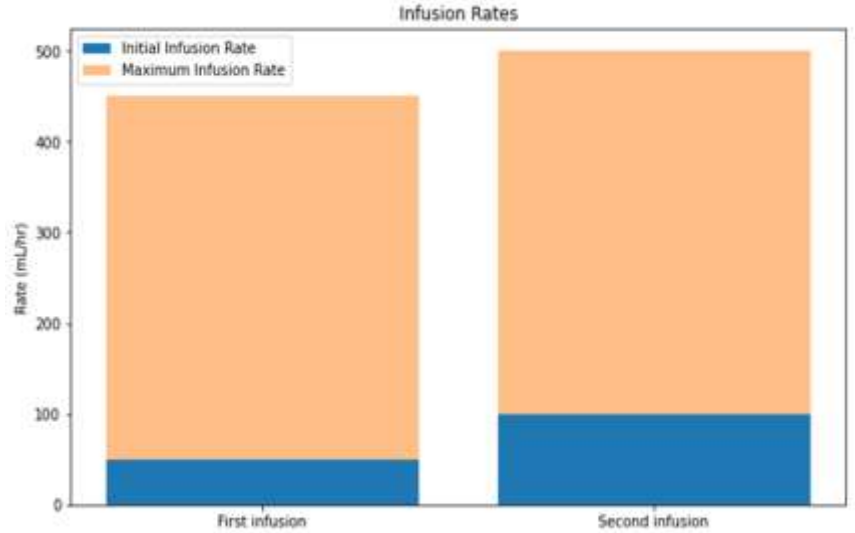
Figure Number	Title	Description/suggested visual
Figure 1	Demographic characteristics of Iraqi patients with moderate-to-severe pemphigus vulgaris.	Bar chart or pie chart showing sex distribution and mean age.
Figure 2	Long-term remission rates over 36 months after rituximab therapy.	Line graph showing remission rates at 3, 6, 12, 18, 24, and 36 months.
Figure 3	Kaplan–Meier survival curve of remission over 36 months after rituximab treatment.	Kaplan–Meier plot showing probability of remission over time.
Figure 4	Changes in antidesmoglein 1 and 3 autoantibody levels before and after rituximab therapy.	Dual-line graph of antibody titers from baseline to 36 months.
Figure 5	Distribution of adverse events among participants over 36 months.	Bar graph showing the incidence of adverse event categories.
Figure 6	Cumulative prednisolone-equivalent corticosteroid exposure during treatment course.	Box-and-whisker plot or histogram of cumulative steroid dose distribution.

Figure 1. Demographic characteristics of Iraqi patients with moderate-to-severe pemphigus vulgaris.



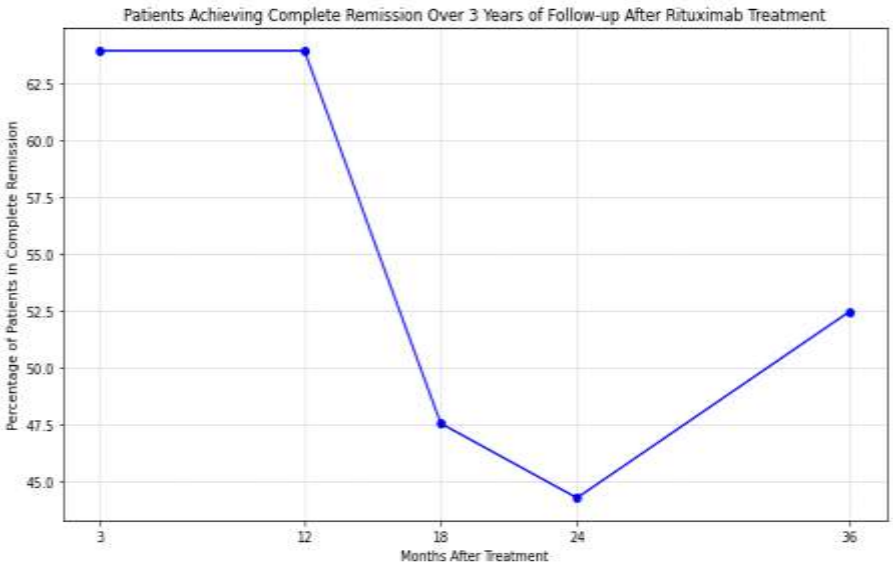
This bar chart illustrates the demographic characteristics of the 61 enrolled participants. The majority of participants were female (55.7%), with a mean age of 41.7 years (±12.3). The chart shows the frequency distribution by sex and age group.

Figure 2. Long-term remission rates over 36 months after rituximab therapy.



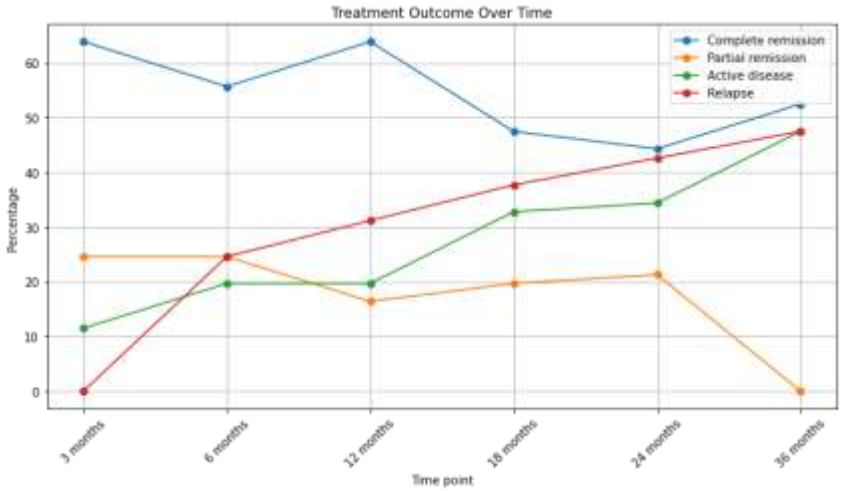
The provided line graph shows the proportion of patients who achieved complete remission at 3, 6, 12, 18, 24, and 36 months. The maximum remission rate was observed at 12 months (63.9%), after which the rate declined gradually over subsequent follow-up visits. Operationally, remission was defined as the absence of new or pre-existing lesions for at least 2 months without systemic therapy.

Figure 3. Kaplan–Meier survival curve of remission over 36 months after rituximab treatment.



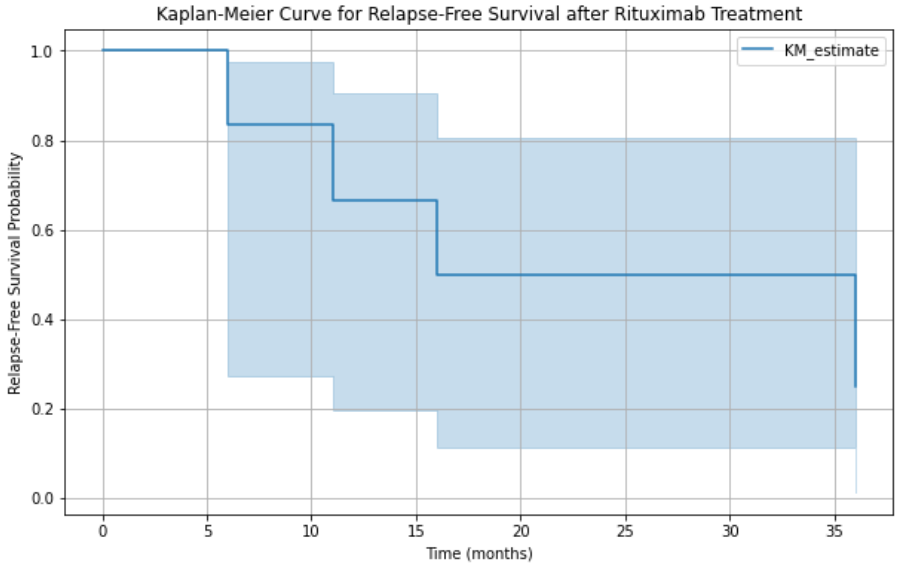
The survival analysis curve tracks 61 patients following rituximab therapy. The relapse-free survival rate was 100% at 6 months and declined to 47.5% at 36 months. Relapse was defined as the occurrence of at least three new nonhealing lesions per month. Censoring events are indicated by tick marks.

Figure 4. Changes in antidesmoglein 1 and 3 autoantibody levels before and after rituximab therapy.



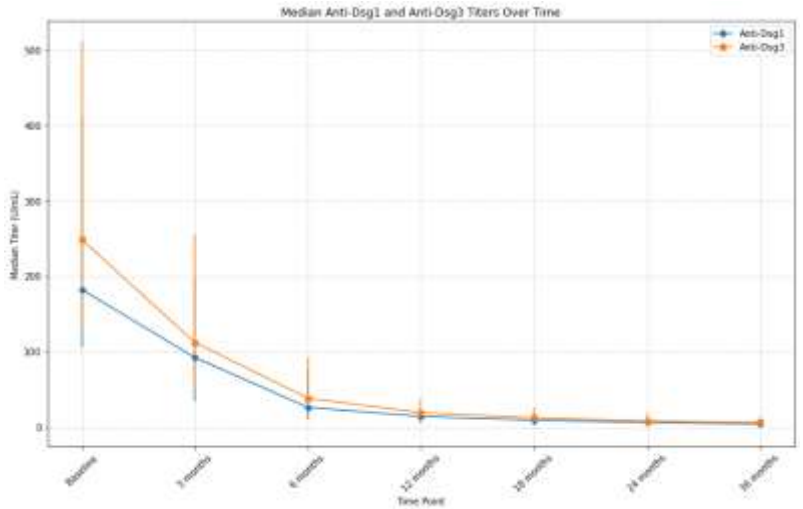
The line graph shows a declining trend in autoantibody levels assessed at baseline and at 3, 6, 12, 18, 24, and 36 months. Both anti-Dsg1 and anti-Dsg3 levels decreased significantly ($p < 0.001$), with the greatest reduction observed during the first 6 months. Antibody concentrations are reported in units/mL, and measurements were performed using enzyme-linked immunosorbent assay techniques.

Figure 5. Distribution of adverse events among participants over 36 months.



The bar chart shows the distribution of adverse events observed during the study, including infusion-related reactions (11.5%), infections requiring antibiotic treatment (4.9%), abnormal liver function test results (3.3%), and hospitalizations (1.6%). No severe adverse events or treatment-related fatalities were reported.

Figure 6. Cumulative prednisolone-equivalent corticosteroid exposure during treatment course.



The box plot illustrates the total prednisone-equivalent corticosteroid exposure over the 3-year course. The median cumulative dose was 220 mg (interquartile range, 0–345 mg). The categories were as follows: no steroid use (34.4%), low-dose use (<100 mg), moderate-dose use (101–500 mg), and high-dose use (>500 mg). This finding highlights the steroid-sparing effect of rituximab.

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