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Rituximab in pemphigus and pemphigoid patients: Treatment outcomes and safety profile - A 6-year tertiary center study

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ABSTRACT

Background: Pemphigus and pemphigoid are autoimmune blistering disorders characterized by autoantibodies attacking skin and mucous membranes. Rituximab, targeting CD20-positive B cells, has emerged as a treatment option for resistant cases. **Aims and Objectives:** To evaluate the treatment outcomes and safety profile of rituximab in patients with pemphigus and pemphigoid diseases treated at a tertiary care center over 6 years. **Materials and Methods:** This retrospective study analyzed the outcomes of 23 patients treated with rituximab for pemphigus and pemphigoid diseases at a tertiary care hospital between February 2017 and February 2023. Data included demographics, disease characteristics, treatment specifics, and adverse reactions. Treatment response was evaluated using the Nikolsky sign, and the World Health Organization causality assessment scale classified adverse events. Statistical analysis was conducted with SPSS version 25.0. **Results:** The study included 23 patients (52.2% male), with a mean age of 50.48 years. Majority of the patients were diagnosed with pemphigus vulgaris (60.9%). Of the 23 patients, 17 (73.9%) achieved complete remission, while 6 (26.1%) attained partial remission. Most patients (43.5%) required two cycles of rituximab, with complete remission achieved after two cycles in 52.9% of those in remission. Patients with partial remission required more infusions, with 33.3% receiving three or more cycles. Adverse drug reactions (ADRs) were observed in 5 patients (21.7%), all of whom experienced mild, infusion-related symptoms, such as pruritus (8.7%) and dyspnea (4.3%). A significant association between gender and ADRs was found, with females more prone to ADRs (P = 0.008). No severe reactions were reported, and all ADRs were resolved. **Conclusion:** Rituximab shows high efficacy in inducing remission in pemphigus and pemphigoid patients, with a manageable safety profile. Individualized treatment regimens, including the number of cycles, may optimize outcomes.

Key words: CD20; Adverse drug reactions; Autoimmune disorders; Remission; Dermatology; Blistering diseases

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INTRODUCTION

Pemphigus and pemphigoid diseases represent a group of potentially life-threatening autoimmune blistering disorders affecting the skin and mucous membranes. These conditions are characterized by the production of autoantibodies against intercellular adhesion molecules in the epidermis, leading to blister formation.[1] The management of these diseases poses significant challenges, including the advanced age of affected patients, the

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presence of comorbidities limiting immunosuppressive treatments, and the lack of effective interventions to prevent scarring.[2]

In recent years, rituximab has emerged as a promising therapeutic option for pemphigus and pemphigoid diseases, particularly in cases resistant to conventional treatments. As a monoclonal antibody targeting CD20-positive B cells, rituximab has demonstrated efficacy in inducing disease remission and improving the quality of life for affected individuals. Studies have shown that approximately 67% of patients exhibit noticeable improvements in disease activity within 6 months of rituximab treatment.[3-5]

However, concerns persist regarding rituximab's long-term safety profile and optimal dosing regimens. The Food and Drug Administration-approved dosing for moderate-to-severe pemphigus vulgaris involves administering rituximab at 1000 mg twice, with a 14-day interval, followed by maintenance doses. Alternative regimens have also been proposed, allowing clinicians to tailor the approach based on individual patient responses.[3]

Safety monitoring of rituximab has revealed potential adverse events, including infusion-related reactions and infections.[6] Recent research has identified risk factors associated with infusion-related reactions, such as male gender and increased body mass index, emphasizing the need for personalized monitoring approaches.[7]

Aims and objectives

To evaluate the treatment outcomes and safety profile of rituximab in patients with pemphigus and pemphigoid diseases treated at a tertiary care center over 6 years.

MATERIALS AND METHODS

This was a retrospective study, spanning 6 years from February 2017 to February 2023, conducted at the department of dermatology and venereology at a tertiary care teaching hospital, on rituximab's efficacy and safety in pemphigus and pemphigoid patients. Data from hospital medical records included demographics, medical history, diagnosis details, treatment specifics, and outcomes. Particular attention was paid to rituximab administration, dosing, treatment cycles, and concomitant medications. Treatment response was assessed using the Nikolsky sign, a clinical indicator. Each patient was followed up for 6 months from the last dose of rituximab. Infusion-related and systemic adverse events documented in case records were collected and categorized by physiological systems. The World Health Organization causality assessment scale was used to evaluate adverse drug reactions (ADRs). Statistical analysis was conducted using SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean and standard deviation, and categorical variables as absolute numbers and percentages. The study adhered to strict ethical standards, obtaining approval from the institutional ethics committee and implementing measures to ensure patient confidentiality.

RESULTS

Patient demographics and characteristics

The study included 23 patients with pemphigus and pemphigoid diseases, 12 (52.2%) male and 11 (47.8%) female. The mean age of the participants was 50.48±17.2 years. The median duration of the disease interquartile range was 2 (23) months (Vide Table 1).

Comorbid conditions were present in 11 patients (47.8%), with diabetes being the most common (26.1%), followed by hypertension (17.4%), heart disease (17.4%), thyroid disorders (8.7%), chronic obstructive pulmonary disease (8.7%), rheumatoid arthritis (4.3%), seizures (4.3%), and dyslipidemia (4.3%) (Vide Table 1).

Disease involvement and diagnosis

Most patients (60.9%) were diagnosed with pemphigus vulgaris, followed by bullous pemphigoid (21.7%) and pemphigus foliaceus (17.4%). The face (60.9%) and chest (65.2%) were the most frequently affected areas, followed by the upper limbs (56.5%), abdomen (52.2%), scalp (39.1%), axilla (43.5%), lower limbs (34.8%), and genitalia (8.7%) (Vide Table 2).

Treatment response

All patients received a standard 1000 mg infusion of rituximab. Of the 23 patients studied, 17 (73.9%) achieved complete remission, while 6 (26.1%) achieved partial

Table 1: Demographic profile of patients with pemphigus and pemphigoid diseases

Characteristics	Values
Age (mean)	50.48±17.162
Duration of disease in months (median, Q1, Q3)	2 (1.5)
Gender	
Female	11 (47.8)
Male	12 (52.2)
Comorbidities	11 (47.8)
Diabetes	6 (26.1)
Hypertension	4 (17.4)
Thyroid diseases	2 (8.7)
Heart disease	4 (17.4)
COPD	2 (8.7)
Rheumatoid arthritis	1 (4.3)
Seizure	1 (4.3)
Dyslipidemia	1 (4.3)

Note: Data are presented as Mean ± Standard Deviation or number (%), as appropriate. COPD: Chronic obstructive pulmonary disease

remission. The number of rituximab cycles administered varied: four patients (17.4%) received one cycle, 10 (43.5%) received two cycles, 7 (30.4%) received three cycles, and 2 (8.7%) received four cycles. Patients received additional infusions if they did not achieve remission after two cycles. Patients with partial remission tended to receive more infusions: 2 patients each received 3 and 4 infusions (33.3% each of partial remission cases) (Vide Table 3).

ADRs

Nine ADRs were observed in 5 out of 23 patients (21.7%). Infusion-related reactions were the most common, affecting 21.7% (n=5) of patients. Specific symptoms (n=23) included pruritus (8.7%), burning sensation (4.3%), dyspnea (4.3%), and anxiety (4.3%). Respiratory infections, nausea and vomiting, headache, and sleep disturbances were reported in 4.3% of patients (Vide Table 4).

The outcome of ADRs was favorable, with all affected patients achieving the resolution of symptoms. No severe or life-threatening reactions were reported, and no fatalities were associated with the treatment. All ADRs were possible according to the WHO causality scale.

Risk factors and safety profile

The analysis of ADRs among patients receiving rituximab treatment revealed a notable difference between male and female patients. In this cohort, ADRs were observed in 45.5% (5 out of 11) of female patients, whereas none of the male patients (0 out of 12) experienced ADRs. A Chi-square test of independence revealed a statistically significant relationship between gender and ADRs (P=0.008).

Table 2: Clinical profile of patients with pemphigus and pemphigoid diseases

Diagnosis	n (%)
Pemphigus vulgaris	14 (60.9)
Bullous pemphigoid	5 (21.7)
Pemphigus foliaceus	4 (17.4)
Parts involved	
Scalp	9 (39.1)
Face	14 (60.9)
Axilla	10 (43.5)
Chest	15 (65.2)
Abdomen	12 (52.2)
Genitalia	2 (8.7)
Upper limb	13 (56.5)
Lower limb	8 (34.8)

Median time to remission

The Kaplan–Meier survival analysis was conducted to estimate the time to remission following the first treatment dose. The median time to remission was 13.0 months (95% confidence interval [CI]: 0.0, 26.576), indicating that half of the patients achieved remission within this period (Vide Figure 1).

DISCUSSION

The study provides significant insights into rituximab's efficacy and safety profile in managing pemphigus and pemphigoid diseases. These diseases are challenging to treat due to their autoimmune nature, which causes skin and mucous membranes to blister, often requiring potent immunosuppressive therapies.

The study found that 73.9% of patients achieved complete remission after rituximab treatment, while 26.1% experienced partial remission. This aligns with previous studies where rituximab demonstrated substantial efficacy in inducing remission in pemphigus vulgaris and other related disorders. For instance, Joly et al., reported similar remission rates in a randomized controlled trial comparing rituximab with prednisone.[4] The current study's findings are consistent with Bamberger et al., who also observed a high remission rate in mucous membrane pemphigoid with rituximab treatment, further supporting its effectiveness.[3]

However, the variation in remission rates across different studies highlights the influence of factors such as disease severity, patient demographics, and specific treatment regimens. In the current study, some patients required up to four cycles of rituximab, suggesting the need for individualized treatment approaches. This variability underscores the importance of tailoring rituximab treatment to patient-specific factors, as also indicated by Ciolfi et al., who called for reconsideration of rituximab dosing regimens in pemphigus vulgaris.[8]

Furthermore, the study's observation that patients who achieved partial remission required more rituximab infusions than those with complete remission aligns with findings from studies like Bamberger et al., who noted the need for additional infusions in patients with refractory disease.[3] This supports the notion that while rituximab is

Table 3: Response to treatment and number of rituximab infusions

Response to treatment	Number of rituximab infusions				Total (%)
	1 (%)	2 (%)	3 (%)	4 (%)	
Complete remission	3 (17.6)	9 (52.9)	5 (29.4)	0 (0.0)	17 (100.0)
Partial remission	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	6 (100.0)
Total	4 (17.4)	10 (43.5)	7 (30.4)	2 (8.7)	23 (100.0)

Table 4: Adverse drug reactions to rituximab

Adverse drug reactions n (%) n=23	
Infusion-related	
Anxiety	1 (4.3)
Burning sensation	1 (4.3)
Dyspnea	1 (4.3)
Pruritus	2 (8.7)
Respiratory infection	1 (4.3)
Nausea and vomiting	1 (4.3)
Headache	1 (4.3)
Sleep disturbances	1 (4.3)
Total number of patients with ADR	5 (21.7)
Outcome of adverse drug reaction (n=5)	
Resolved	5 (100)

ADR: Adverse drug reactions

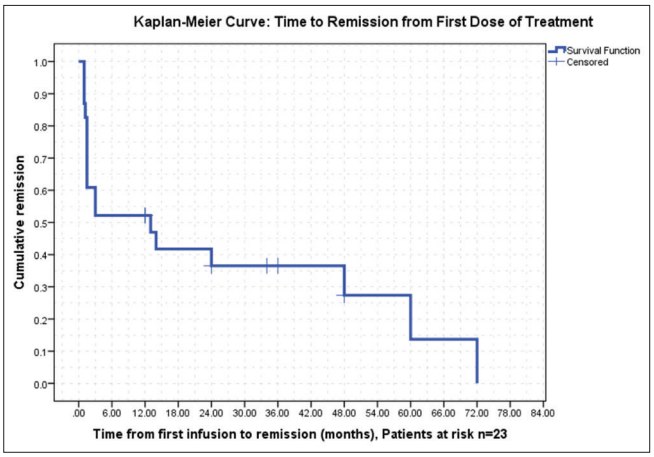

Figure 1: Time to remission from first dose of rituximab infusion

effective, optimizing the number and timing of infusions is crucial for achieving the best outcomes.

The current study found that 43.5% of patients reached complete remission after two infusions of rituximab, suggesting a "sweet spot" where this regimen may be sufficient for many patients, although additional cycles were necessary for some. Comparatively, Joly et al., in the Ritux 3 trial observed a faster median remission time of 3 months when rituximab was combined with short-term prednisone,[4] Ahmed et al., reported a median time of 8 weeks for complete remission, which aligns closely with the current study.[5] Bamberger et al., noted variability in remission times among mucous membrane pemphigoid patients, with some responding within weeks and others taking several months,[3] reflecting the varied response times observed in the current study. In contrast, De et al., reported a longer mean time to remission of around 6 months in Indian pemphigus patients, suggesting that factors such as patient demographics, disease severity, and genetic differences may influence remission times.[9]

The study also highlighted the occurrence of ADRs, with infusion-related reactions being the most common, affecting 21.7% of the patients. This is slightly lower than what Lamberts et al., reported, who noted a higher incidence of adverse events in their study on recalcitrant pemphigoid diseases.[6] The lower incidence of ADRs in the present study could be due to differences in patient populations, rituximab dosing schedules, or the concurrent use of premedications aimed at reducing infusion reactions.

Interestingly, the study found a statistically significant relationship between gender and ADRs, with female patients showing a higher incidence of these reactions. This finding contrasts with the analysis by Nishiura et al., which identified male gender as a risk factor for infusion-related responses in a different patient cohort.[7] The difference may stem from variations in study design, patient characteristics, or the specific autoimmune conditions being treated. This discrepancy highlights the need for further research to better understand the factors influencing rituximab's safety profile in different patient groups.

The safety profile of rituximab observed in this study is broadly consistent with previous research, albeit with some variations in the frequency and severity of ADRs. For instance, a study by Ahmed et al., reported a higher rate of severe infusion reactions and infections than the current study, which reported no severe or life-threatening ADRs.[5] This difference could be attributed to advancements in supportive care and premedication protocols over the years, which have likely reduced the incidence of severe reactions.

The median time to remission in the present study was 13.0 months (95% CI: 0.0, 26.576) following the first dose of rituximab, which is notably longer than reported in several external studies. For instance, Joly et al., in the Ritux 3 trial, observed a median remission time of 3 months when rituximab was combined with short-term prednisone, suggesting that adjunct corticosteroid therapy may significantly expedite remission.[4] Similarly, Ahmed et al., reported a median remission time of 8 weeks (~2 months), reinforcing the idea that rituximab's efficacy can be enhanced with combination regimens.[5] In contrast, Bamberger et al., noted substantial variability in remission times among patients with mucous membrane pemphigoid, with some achieving remission within weeks, while others required several months, which aligns with the wide CI observed in the current study.[3] Meanwhile, De et al., reported a mean remission time of approximately 6 months in Indian pemphigus patients, which, though shorter than in the present study, is still relatively prolonged compared to Western cohorts, possibly due to demographic and genetic factors.[9] The variation in remission times across studies suggests that factors such

as the retrospective nature of the study, disease severity, patient demographics, and treatment regimens, particularly the use of adjunct immunosuppressants, play a crucial role in determining the time to remission. The present study's findings underscore the need for individualized treatment approaches, optimizing the number of rituximab cycles, and considering combination therapies to achieve faster remission.

Limitations of the study

This study was retrospective in nature and relied on data extracted from medical records, which may have resulted in incomplete or inconsistent documentation, particularly regarding adverse drug reactions and long-term outcomes. The sample size was relatively small (n=23), limiting the statistical power and generalizability of findings. Additionally, the absence of a control group and variability in treatment cycles make it difficult to establish causal relationships or standardize outcome measures.

CONCLUSION

The study provides valuable insights into the real-world application of rituximab in treating pemphigus and pemphigoid diseases, confirming its efficacy and manageable safety profile. The findings are consistent with the broader literature, although they highlight the need for individualized treatment regimens to maximize efficacy and minimize adverse events. Further prospective studies with larger cohorts are necessary to refine these treatment protocols and explore the long-term outcomes of rituximab therapy in this patient population.

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