EFFICACY OF RITUXIMAB FOR PEMPHIGUS AT NATIONAL HOSPITAL OF DERMATOLOGY AND VENEREOLOGY IN VIETNAM

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ABSTRACT

Objectives: Rituximab induces a rapid remission in most patients with pemphigus. To evaluate the efficacy and adverse effects of rituximab in the treatment of pemphigus at the Vietnam National Hospital of Dermatology and Venereology.

Methods: A retrospective study was conducted on 41 patients with pemphigus who attended our hospital between 2019 and 2024. Each enrolled patient received two doses of rituximab (1000mg per dose) administered as intravenous infusions two weeks apart. Subsequently, a maintenance dose of 1000mg was administered intravenously at month 6 or 12, followed by every 6 months based on clinical evaluation. The efficacy and safety of the treatment were assessed through pemphigus disease area index (PDAI) evaluations conducted before and after therapy, monitoring clinical responses, and recording any adverse events during follow-up.

Results: 41 patients with pemphigus (pemphigus vulgaris: 39 patients, pemphigus foliaceus: 2 patients) who were treated with rituximab and followed for a median period of 20.5 months. The average patient age was 49.2 years, with males representing 31.7% of the cohort. The mean number of infusions administered per patient was 3.02. Complete remission was achieved in 32 (78%) patients, and all patients responded to treatment. The mean time to achieve disease control and complete remission was 4.8 ± 1.1 weeks and 8.2 ± 3.8 months, respectively. Relapse occurred in six (14.6%) patients after an average duration of 17.0 ± 2.5 months. One patient developed pneumonia as an infectious complication and subsequently died.

Conclusions: Rituximab is a highly effective therapeutic agent for the management of pemphigus. It enables rapid disease control and achieves high rates of complete remission.

Keywords: *Pemphigus; rituximab; immune bullous disease.*

1. INTRODUCTION

Pemphigus is a rare, chronic autoimmune blistering diseases characterized by the formation of blisters on the skin and mucous membranes.[1,2] These conditions are caused by autoantibodies that target desmosomal proteins, leading to the separation of epidermal cells. Pemphigus

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can significantly impact a patient's quality of life due to pain, discomfort, and the potential for secondary infections. While various treatments have been used, including corticosteroids and immunosuppressants, their long-term use can be associated with significant side effects.[3]

Rituximab, a monoclonal antibody targeting B cells, has emerged as a promising therapeutic option for pemphigus, demonstrating efficacy in inducing rapid remission in many patients.[4-6] In June 2018, the FDA approved rituximab for the treatment of adult patients with moderate to severe pemphigus. Rituximab is the first biologic therapy approved by the FDA for pemphigus and represents the first major advancement in the treatment of the disease in more than 60 years.4 S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV, 2020) used rituximab as the first line treatment for all severity levels of disease.[7]

This study aimed to evaluate the efficacy and adverse effects of rituximab in pemphigus patients treated at the Vietnam National Hospital of Dermatology and Venereology from 2019 to 2024. This research contributes to the expanding body of evidence supporting the use of rituximab in pemphigus and provides valuable data specific to the Vietnamese patient population.

2. MATERIALS AND METHODS

2.1. Study subjects

41 patients diagnosed with pemphigus were treated with a rituximab regimen for at least the first cycle (days 1 and day 15). The inclusion criteria included individuals aged 18 years or older who met the primary diagnostic standards for pemphigus at the National Hospital of Dermatology and Venereology from January 2019 to June 2024, with complete medical records. Exclusion criteria included pregnant or lactating women.

2.2. Study methods

Study design

This is a cross-sectional study comprising a retrospective review of records and photographs of all eligible patients, along with a prospective follow-up of pemphigus patients indicated for rituximab.

Procedures

The examination and selection of patients are based on the assessment of disease severity (PDAI) and IgG autoantibody concentration by indirect immunofluorescence. The Rituximab treatment regimen follows the protocol for pemphigus patients issued by the National Hospital of Dermatology and Venereology. Induction therapy includes Rituximab 1000 mg on days 1 and 15, combined with tapering of the glucocorticoid dose. Maintenance therapy consists of Rituximab 1000 mg after the induction dose for 6 months, followed by repeated doses every 6 months or based on clinical assessment. In case of relapse, Rituximab 1000 mg is administered when the patient relapses, and consideration is given to reinitiation or escalation of the glucocorticoid dose depending on the clinical status. Follow-up includes the assessment of treatment outcomes and clinical and laboratory ADRs (adverse drug reactions) after 3, 6, and 12 months.

Outcomes

Treatment results are evaluated after 3, 6, and 12 months. Clinically, disease progression is assessed based on the PDAI index. The time at which the patient achieves disease control, defined as the interval from baseline to the point when new lesions cease to form and established lesions begin to heal, is determined. Complete

remission off therapy is defined as the absence of new and/or established lesions while the patient is off all systemic therapy for at least two months. Complete remission on therapy is defined as the absence of new or established lesions while the patient is receiving minimal therapy, which is ≤ 10 mg/day of prednisone (or the equivalent) and/or minimal adjuvant therapy for at least two months. Minimal adjuvant therapy is defined as half the dose required to be considered treatment failure. Partial remission off therapy is defined as the presence of transient new lesions that heal within one week without treatment, while the patient is off all systemic therapy for at least two months. Partial remission on minimal therapy is defined as transient new lesions that heal within one week while the patient is receiving minimal therapy, including topical steroids. Relapse and flare of disease are synonymous and are defined by the appearance of three or more new lesions per month that do not heal spontaneously within one week or by the extension of established lesions in a patient who has achieved disease control. Therapy failure is defined as the inability to control disease activity (i.e., relapse/flare) with full therapeutic doses of systemic treatments. Adverse effects include fatigue, vomiting, nausea, abdominal pain, acne, skin atrophy, telangiectasia, Cushing's face, and changes in blood tests (blood count, glucose, liver enzymes [GOT, GPT], kidney function [urea, creatinine, urine]). The cumulative dose of corticosteroids for each patient is recorded, as well as the quantitative value of IgG autoantibody concentration by the indirect immunofluorescence method.

Statistical analysis

Statistical analysis was performed using non-parametric tests, with statistical significance at the 95% confidence level ($p < 0.05$). The calculations were performed using the SPSS 20.0 and Excel 2019. Statistical comparisons for qualitative variables within the same group used the McNemar's test; comparisons between two groups used the Chi-square test, with Fisher's exact test applied if the expected value was less than 5. For quantitative variables, T-tests were used to compare means between two independent samples.

2.3. Ethics

Personal information of patients was kept confidential and used solely for the purpose of this study, in accordance with the 2013 Helsinki guidelines. This study was approved by the National Hospital of Dermatology and Venereology. This was a descriptive study, without intervention, so it did not affect the progress or treatment methods for patients.

3. RESULTS

3.1. Patient characteristics

A total of 41 patients with pemphigus were included, with demographic information available in Table 1.

Table 1. Demographic characteristics for the 41 subjects

Characteristic	Value
Age, median (range)	*49.2 ± 12.4 (18 - 68)*
Sex, n (%)	
Male	*13 (31.7%)*
Female	*28 (68.3%)*

Characteristic	Value
Type	
Pemphigus vulgaris	39 (95.1%)
Pemphigus foliaceus	2 (4.9%)
Onset time	27.5 ± 20.7 months (4 - 120)
PDAI	34.8 ± 26.1 (2 - 154)
Systemic medicals taken before	
Corticoid	41 (100%)
Azathioprin	13 (31.7%)
Rituximab	1 (2.4%)
MMF	1 (2.4%)

3.2. Serum IgG antibody titer dilution level

Among them, 39 had pemphigus vulgaris, and 2 had pemphigus foliaceus. All patients had previously been treated with glucocorticoids. One patient with pemphigus foliaceus had received rituximab treatment but discontinued it for 2 years before experiencing a relapse. An indirect immunofluorescence assay was performed on 31 patients to measure serum IgG antibody titer. The Pearson correlation coefficient between IgG antibody titer and disease severity (PDAI) was 0.299, indicating a low correlation (Figure 1).

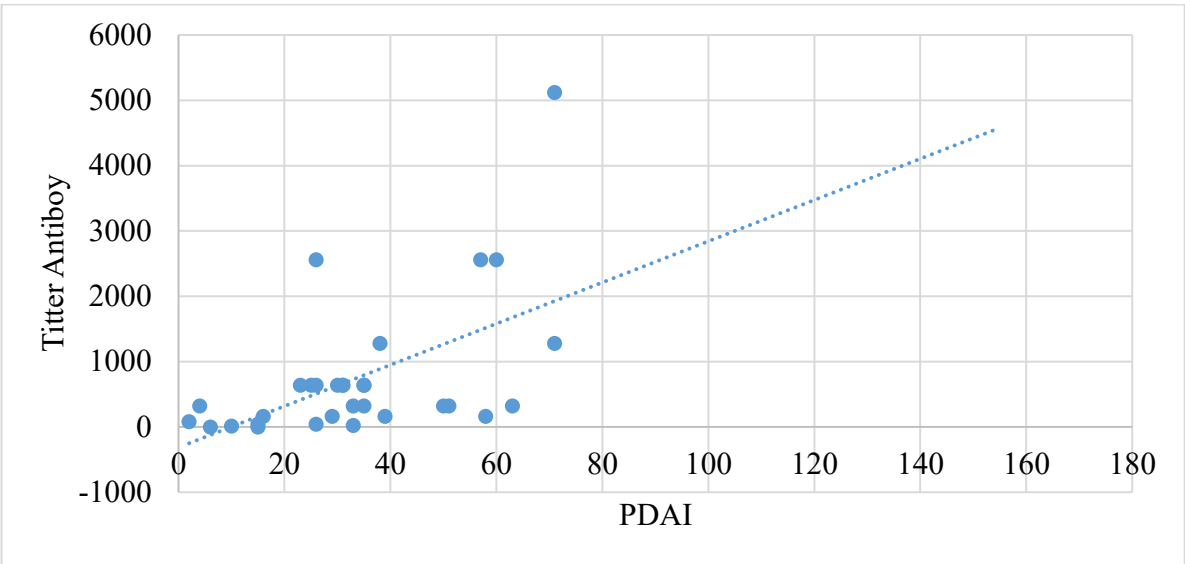

Figure 1. Serum IgG antibody titer dilution level (n = 31)

3.3. Treatment Response to Rituximab

All patients received a minimum of two doses of rituximab (administered on days 1 and 15). Of these, 15 patients were treated twice, 14 patients received three treatments, 8 patients underwent four treatments, and 4 patients were treated five times. The average number of infusions was 3.0. The follow-up period was 20.5 ± 10.6 months.

The time to achieve outcomes is shown in Table 2. After the first rituximab cycle, all patients controlled disease activity at a median of 4.8 ± 1.1 weeks. Complete remission was seen in 78% of patients (32 out of 41) at a median of 8.2 ± 3.8 months. Eight patients achieved partial remission. Relapse occurred in 14.6% of patients (6 out of 41) at a median of 17.0 ± 2.5 months post-treatment.

Table 2. Treatment response to Rituximab

Endpoint	n	%	Time period to achive event (Mean)
Control of disease activity	41	100.0	4.8 ± 1.1 weeks
Complete remission	32	78.0	8.2 ± 3.8 months
Complete remission off therapy	24	58.5	8.2 ± 3.8 months
Complete remission on therapy	8	19.5	8.0 ± 3.7 months
A partial remission	8	19.5	
Relapse	6	14.6	17.0 ± 2.5 monhts
Failure of therapy	0	0	

3.4. Change in PDAI severity score over time

The severity of the disease is clearly expressed by the PDAI scale (Figure 2). The median baseline PDAI scores were 34.8 ± 26.1 (n = 41) and PDAI at third month were 6.8 ± 11.2 (n = 40). The difference in PDAI between the first and third months was statistically significant with $p < 0.001$ (pair sample T Test).

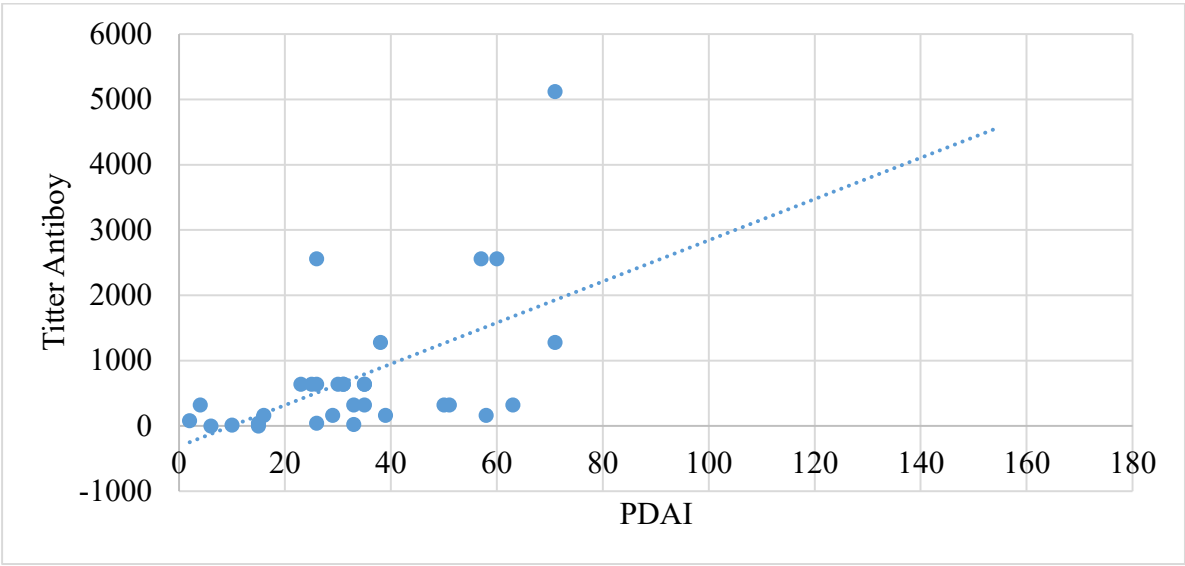

Figure 2. Change in PDAI severity score over time

3.5. Changes in baseline corticosteroid dosage and serum IgG antibody titters over time

The changes in the baseline corticosteroid dosage (methylprednisolone) during the study period, when used in conjunction with rituximab therapy, is a significant factor in assessing treatment response. It is important to note that methylprednisolone was the primary systemic corticosteroid used in this cohort. All patients received concurrent immunosuppressive therapy with methylprednisolone; no other immunosuppressants (azathioprine, mycophenolate mofetil, etc.) were used.

At the initiation of rituximab therapy (baseline), the mean daily dose of methylprednisolone was 46.4 ± 21.4 mg and significantly decreased to 15.4 ± 10.4 mg/day at the 3rd month with $p < 0.001$ (Pair sample T Test). It continued to decrease at the sixth month (5.7 ± 6.8 mg/d, n = 40) and the twelfth month (3.5 ± 6.3 mg/d, n = 33) (Figure 3).

Serum IgG antibody titters also showed a significant reduction post-treatment. Among the 18 patients tested for serum IgG antibody titer, the pretreatment serum IgG antibody titer dilution level decreased significantly from 600.6 ± 781.5 at baseline to 87.7 ± 300.3 at the sixth month ($p = 0.022$).

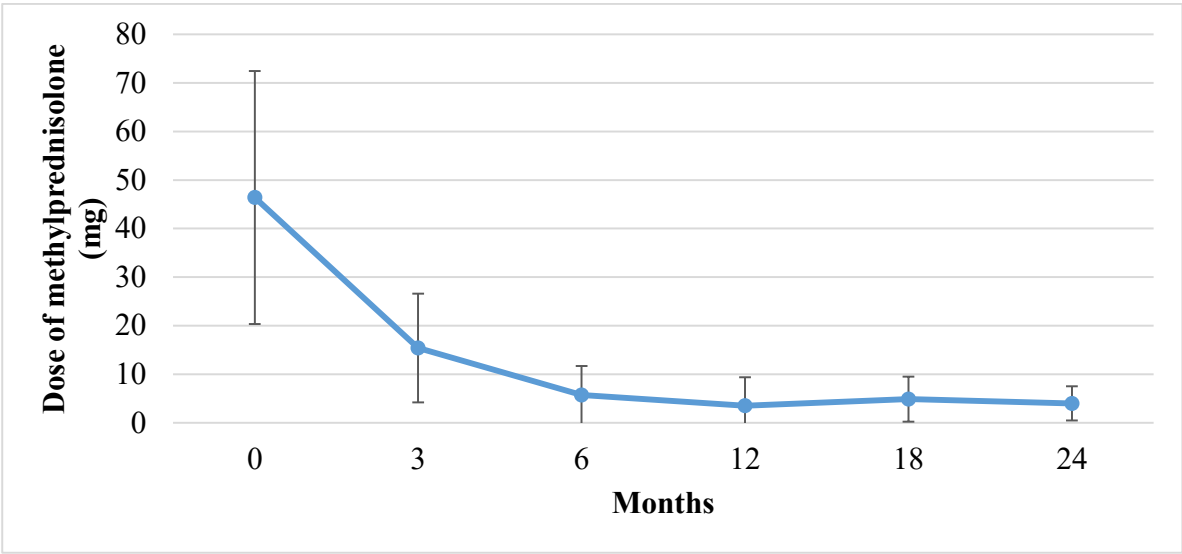

Figure 3. Methylprednisolone dose changes over time

3.6. Adverse effects of rituximab

Table 3 summarizes the adverse effects observed in 41 patients with pemphigus who received rituximab treatment. The most common side effect was fatigue (4.9%), followed by pneumonia (4.9%). Less frequent side effects included cardiovascular disorders (2.4%) and shortness of breath (2.4%). Notably, several potential side effects were not observed in this patient group, including rash, digestive symptoms, blurred vision, hematological disorders, and virus infection. One of our patients died after 2 months of treatment due to pneumonia. This patient had completed 1 cycle of rituximab with good response, after 2 months developed pneumonia and died at the provincial hospital. We did not determine the relationship between rituximab use and death in this patient.

Table 3. Adverse effects of rituximab

Side effects	n (patient)	%
Tired	2	4.9
Rash	0	0
Cardiovascular disorders	1	2.4
Digestive symptoms	0	0
Shortness of breath	1	2.4
Blurred vision	0	0
Pneumonia	2	4.9
Hematological disorders	0	0
Virus infection	0	0

4. DISCUSSION

This retrospective study assessed the efficacy and safety of rituximab in 41 pemphigus patients treated at the Vietnam National Hospital of Dermatology and Venereology between 2019 and 2024. The results indicate that rituximab is an effective treatment for pemphigus, achieving rapid disease control and high rates of complete remission, aligning with findings from previous studies.

The 78% complete remission rate observed in our cohort is consistent with the established efficacy of rituximab in pemphigus. This response rate demonstrates the drug's significant impact on disease activity. The mean time to disease control was 4.8 ± 1.1 weeks, and complete remission occurred within 8.2 ± 3.8 months, indicating a relatively quick onset of action for rituximab. This offers patients timely relief from their symptoms. Additionally, all patients in our study responded to treatment, even if complete remission was not achieved, indicating the broad applicability of rituximab in this patient population. The Ritux 3 study was a phase 3 clinical trial involving two groups of patients: 46 patients received rituximab combined with prednisolone, while 44 patients were administered prednisolone alone.[5] The 3-year follow-up results revealed that 89% of patients in the rituximab group achieved remission at 24 months, compared to only 28% in the prednisolone-only group. Furthermore, a retrospective study conducted in 2021 on 117 patients who had received at least one cycle of rituximab (1000 mg on days 0 and 14) demonstrated that 74% of patients achieved remission after one cycle, with a median duration of 5.5 months.[6] Relapse was observed in 49% of these patients, with a median duration of 18 months.

The study also examined the relapse rate, which is crucial for evaluating long-term efficacy. The observed 14.6% relapse rate after a mean duration of 17.0 ± 2.5 months aligns with the range reported in other studies. This data informs clinicians about the potential for disease recurrence and the necessity for ongoing monitoring and potential retreatment strategies. Understanding the relapse pattern aids in tailoring follow-up schedules and addressing potential disease flares proactively.[8,9]

The average number of rituximab infusions received by our patients was 3.02. This suggests that the majority of patients in our cohort achieved sustained disease control with a relatively limited

number of treatment cycles. This is an important consideration from both a patient convenience and a healthcare resource utilization perspective. Limiting the number of infusions minimizes the burden on patients and reduces healthcare costs associated with repeated treatments.

This study demonstrates the significant steroid-sparing effect of rituximab in pemphigus patients. The substantial decrease in mean daily methylprednisolone dose from 46.4 ± 21.4 mg at baseline to 15.4 ± 10.4 mg at 3 months ($p < 0.001$) highlights the rapid impact of rituximab on disease activity. This reduction is crucial for minimizing the long-term adverse effects associated with prolonged high-dose corticosteroid use. The continued decline in mean methylprednisolone dose at 6 months (5.7 ± 6.8 mg) and 12 months (3.5 ± 6.3 mg) further emphasizes the sustained efficacy of rituximab, enabling progressive steroid withdrawal. This indicates that rituximab not only achieves initial disease control but also supports long-term maintenance with significantly reduced steroid usage. The Ritux 3 study demonstrated that rituximab effectively reduced the cumulative prednisone dose to 5800 mg compared to 20520 mg in the control group, while also minimizing the side effects associated with corticosteroids.[5]

Furthermore, we observed a significant decrease in serum IgG antibody titers following rituximab treatment. The mean pretreatment titer of 600.6 ± 781.5 decreased significantly to 87.7 ± 300.3 at 6 months ($p = 0.022$). This reduction in autoantibody levels likely contributes to the observed clinical improvements and supports the proposed mechanism of action of rituximab, namely B-cell depletion and subsequent reduction in pathogenic autoantibody production. Other studies around the world often use anti-desmoglein 1 and antidesmoglein 3 as markers of disease activity.[10,11] However, the limited sample size ($n = 18$) for IgG titer measurements warrants caution in interpreting these results. Future studies with larger cohorts are needed to confirm these findings and further investigate the correlation between IgG titer reduction and anti-desmoglein 1, antidesmoglein 3 and clinical response in pemphigus patients treated with rituximab.[12,13]

While our results highlight the significant benefits of rituximab, it is essential to acknowledge possible adverse events. Common side effects include immediate infusion reactions (urticaria, tachycardia, tachypnea) and infectious complications (herpes zoster, CMV, pneumonia).[14] In our study, one patient developed pneumonia, which unfortunately proved fatal.

This serious infection risk is known with rituximab, especially in immuno-compromised individuals[7,15]. This case emphasizes the need for careful patient selection, thorough pre-treatment evaluations, and vigilant monitoring during and after administration. Further research with larger samples is necessary to better understand rituximab's safety profile in pemphigus patients and to identify potential risk factors for adverse events.

This study presents several limitations. The retrospective design introduces potential biases, including recall bias and selection bias. Additionally, the relatively small sample size may constrain the generalizability of our results. Prospective studies with larger and more diverse patient populations are warranted to validate these findings and to further investigate the long-term efficacy and safety of rituximab in treating pemphigus. Furthermore, this study primarily focused on clinical outcomes without incorporating other potentially significant measures such as quality of life assessments. Future research should include these metrics to provide a more comprehensive understanding of rituximab's impact on patients with pemphigus.

Despite these limitations, our study provides valuable real-world data supporting the use of rituximab in Vietnamese pemphigus patients. The high rates of complete remission, rapid disease control, and manageable relapse rate highlight the significant clinical benefits of this therapy. Our findings contribute to the growing body of evidence supporting rituximab as a first-line treatment option for pemphigus and reinforce its role in improving patient outcomes. Further research is needed to optimize treatment protocols, minimize adverse events, and further explore the long-term impact of rituximab in this challenging disease.

5. CONCLUSIONS

Our research confirms that rituximab is an effective treatment for pemphigus, demonstrating rapid disease control and high rates of complete remission. Nevertheless, additional studies are required to validate these results and to further investigate the long-term safety and efficacy of rituximab in the management of pemphigus.

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