ORIGINAL RESEARCH

Effectiveness and Safety analysis of rituximab in the treatment of pemphigus

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ABSTRACT
Background: Pemphigus is a group of potentially fatal autoimmune mucocutaneous blistering diseases. Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody being increasingly used and becoming the first-line therapy in the management of pemphigus.**Aim:** To evaluate the efficacy and safety of rituximab in patients of pemphigus vulgaris (PV) who either did not respond or relapsed after conventional therapeutic regimens and in treatment naive pemphigus patients. **Methods:** The study included pemphigus patients coming to the tertiary health care centre, Jaipur between January 2020 and December 2022. All enrolled patients received two doses of rituximab (1 gram in each) as intravenous infusions two weeks apart as per the rheumatoid arthritis protocol. The efficacy and safety were evaluated by assessing pemphigus area and activity score (PAAS) before and after the therapy, clinical response and any adverse events during follow-up. **Results:**Twenty Two (fifteen males and seven females) patients were included in the study. The age of these patients ranged from 27 to 60 years, with a mean of 43.8 ± 9.8 years. There were 21 (95.45%) patients with PV (20 mucocutaneous type and 01 mucosal) and 1 (4.6%) with pemphigus foliaceus. Among these patients, 15 (56.25%) were relapse cases, 4 (25%) were non-responders, and 3 (18.75%) were fresh cases who received rituximab as first-line therapy. Fourteen (87.5%) patients reached complete remission off therapy over a median time of 6.36 months. Rituximab was well-tolerated by our patients, and no serious adverse events were observed. **Conclusion:** Rituximab had demonstrated a robust and long-lasting response in individuals with PV following a single course and has an excellent safety and tolerability profile.
Key words: Pemphigus, rituximab, anti CD20 monoclonal antibody

INTRODUCTION

Pemphigus is a potentially life-threatening chronic autoimmune bullous disease caused by autoantibodies directed against the cell surface protein desmogleins (Dsg).[1-3] The disease is characterized by mucocutaneous blisters and erosions.[4,5] Systemic corticosteroids have been considered as the traditional treatment of choice, as they have a high probability of decreasing the mortality rate.[6,7] However, long-term use at a high dose is often required, resulting in potential adverse effects.[8] The combination of systemic corticosteroids with other immunosuppressive agents, e.g. azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide, cyclosporin, and methotrexate, has been proven to be effective, as this approach possesses a steroid-sparing effect and may induce complete clinical remission in pemphigus.[9-13] Nevertheless, the remission rate is not satisfactory, and a significant number of patients experience relapse following treatments. Intravenous immunoglobulin and plasmapheresis have been employed in the treatment of autoimmune bullous disease, including pemphigus vulgaris; however, the results remain inconsistent.[14-17]

A major development in pemphigus treatment came with the use of rituximab, a chimeric murine/human monoclonal immunoglobulin G1 antibody that targets CD20, which is a B-cell differentiation marker.[18] Rituximab selectively acts on the CD20-expressing B-cells, which are known to secrete antibodies targeting Dsg.[18] Heizmann *et al*., used rituximab for the first time in treatment of autoimmune bullous diseases and

reported a case of paraneoplastic pemphigus successfully treated by rituximab.[19] Though initially used as an off-label agent in the treatment of pemphigus since then, rituximab has been increasingly used and has revolutionized the treatment of immunobullous diseases resulting in the major shift of focus from more global immunosuppression to targeted immunotherapy and is now a days recommended as first-line treatment, especially for the treatment of naïve pemphigus patients.[20] This has a steroid-sparing effect and an effective treatment for pemphigus.As a result, rituximab has been approved by the US Food and Drug Administration and the European Academy of Dermatology and Venereology as a first- line treatment for moderate to severe pemphigus.[19,20] When used as the first-line treatment, rituximab can provide a high clinical remission rate of approximately 70-80%, as reported in studies on Caucasians.[21-23] However, there is limited data regarding its use in Southeast Asia, and a consensus regarding the use of rituximab for Asian pemphigus patients is still lacking.

With this study, we intended to present our experience with fixed-dose rituximab therapy in pemphigus from a tertiary care hospital in East-cental part of rajasthan.

METHODS

The study was conducted in the department of Dermatology, Venereology, and Leprosy involving patients with pemphigus (fresh, relapse, and recalcitrant cases) who received rituximab from January 2019 to Sep. 2022. Twenty Two (fifteen males and seven females) patients were included in the study. The age of these patients ranged from 27 to 60 years, with a mean of 43.8 ± 9.8 years. Written informed consent was obtained from each patient.

Diagnosis of pemphigus was made based on Tzanck smear, histopathologyand direct immunofluorescence findings. Data regarding the disease, any co-morbidities, previous treatments received, response to treatment, and any adverse events were recorded. Disease severity assessment in pemphigus patients was done using the Pemphigus Area and Activity Score (PAAS) at the beginning of the therapy and on every subsequent visit.

In each patient hemogram, routine biochemical investigations, electrocardiogram (ECG), Mantoux test, and serology for viral hepatitis and human immunodeficiency virus were performed. Exclusion criteria for rituximab therapy were:

i) Pregnancy.
ii) Breastfeeding.
iii) History of sensitization to murine protein.
iv) Active and/or severe infections (including tuberculosis, sepsisand viral hepatitis).
v) Severe cardiac disease.

Rituximab was administered using a fixed-dose (rheumatoid arthritis) protocol, 1 g intravenously on days 1 and 15. Rituximab infusion was given after pre-medications (hydrocortisone, pheniramine, and paracetamol) under strict monitoring over a period of 5-6 hours. After the rituximab infusions, patients were evaluated at monthly intervals for at least six months. Patients already receiving corticosteroids and/or other immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil) at the time of rituximab infusion were continued with the respective medications post-infusion, while the patients not on any form of therapy at the time of infusion were started on oral prednisolone at a dosage of 0.5 mg/kg of body weight post-infusion. Based on clinical improvement.

PRE-RITUXIMAB EVALUATION: Complete hemogram, Liver function tests, Renal function tests, Viral markers- HBV, HCV, HIV-1 and HIV-2, Chest X ray, Mantoux test and chest CT, ECG and echocardiography.

PRE-MEDICATION: Hydrocortisone 100 mg IV, Pheniramine maleate 25 mg IV, Ondansetron 8 mg IV, Ranitidine 50 mg IV, Paracetamol 500 mg oral.

RITUXIMAB TREATMENT:1000 mg of rituximab was diluted in 500 mL of 0.9% normal saline, First infusion (Day 0): 50 mg⁄h, 30-min escalation of 50 mg ⁄ h, maximum infusion rate of 400 mg ⁄ h, total infusion time: 5–6 h, Second infusion at day 15.

RESULTS

Total Twenty-two patients were included in the study comprising fifteen males and seven females patients were included in the study. The age of these patients ranged from 27 to 60 years, with a mean of 43.8 ± 9.8 years. There were 21 (95.4%) patients with pemphigus vulgaris (PV) (20 mucocutaneous type and 01 mucosal) and 1 (4.6%) with pemphigus foliaceus. Among these patients, 15 (56.25%) were relapse cases, four (25%) were non-respondersand three (18.75%) were fresh cases who had not received any prior systemic treatment with corticosteroids or immunosuppressives (treatment naïve cases) and received rituximab as first-line therapy. The duration of the disease at the time of rituximab infusion ranged from 4 to 85 months, with a mean duration of 29.9 ± 25.5 months. 19 (86.3%) patients were on systemic corticosteroids (dose ranging from 0.5-1 mg/kg of prednisolone) and/or other immunosuppressive drugs (cyclophosphamide, azathioprine, MMF) at the time of rituximab infusion. The PAAS score at baseline ranged from 6.7 to 28.8, with a mean of 15.7 ± 6.7 [The various patient characteristics are enumerated in Table 1]. The mean follow-up time after the first rituximab infusion was 14.92 ± 6.47 months (ranging from 9 to 25 months). 19 (86.3%) patients reached complete remission (CR) off therapy over a median time of 6.36 months (ranging from 18 weeks to 35

weeks). Three (13.63%) patients achieved only a partial response and had to receive a maintenance dose (500 mg) at six months post-therapy. The mean time for achieving CR off therapy in patients (n=3) who received rituximab as first-line therapy was 4.3 months, which was significantly lower than those receiving it as second-line therapy (p<0.05). The PAAS score at six months post rituximab ranged from 0 to 4.2, with a mean of 1.7 ± 1.5. The reduction in mean PAAS from baseline was statistically significant (p<0.05). Among patients achieving complete remission (n = 19), relapse occurred in three (15.7%) patients at 14, 16 and 17 months respectively (mean 15.5 ± 2.12 months). These three patients received a second cycle of rituximab therapy, currently in partial remission while on therapy (prednisolone/azathioprine).

Table 1: Patient characteristics

Total Number of patients=22	
Characteristics of pemphigus patients	
Gender	
Male	15
Female	7
Age [Mean, (Range)]	43.8±9.8 (27 to 60 years)
Diagnosis	
Pemphigus vulgaris	21 (95.45%)
Mucocutaneous	20 (95.23%)
Mucosal only	01 (4.7%)
Pemphigus foliaceus	1 (4.54%)
Baseline PAAS [mean, (range)]	15.7±6.7 (6.7 to 28.8)
Underlying disease	
Hypertension	3
Diabetes mellitus	2
Dyslipidemia	1
Disease duration before receiving rituximab	29.9±25.5 months (4 to 85 months)
Patient category, *n* (%)	
First-line therapy (Fresh cases)	3 (18.75%)
Second/third-line therapy (Relapse and recalcitrant cases)	19 (86.36%)

Fig1: Multiple Erythmatous erosion and crusting on face

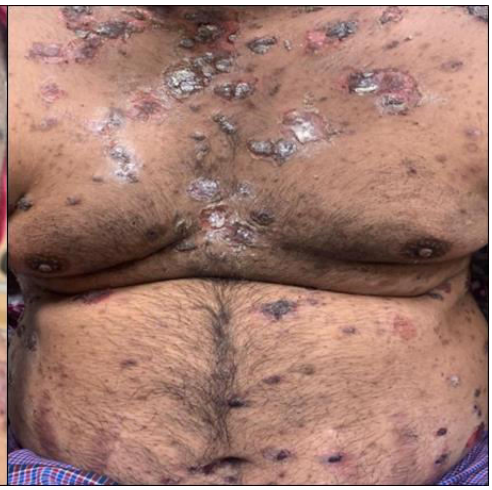

Fig. 2: Multiple Erythmatous erosion and crusting on Trunk

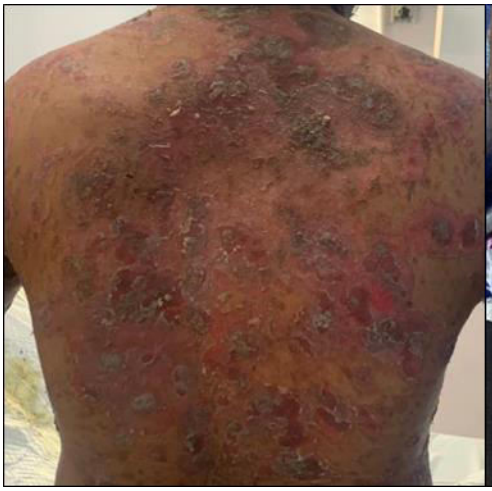

Fig3: Multiple Erythmatous erosion and crusting on Trunk

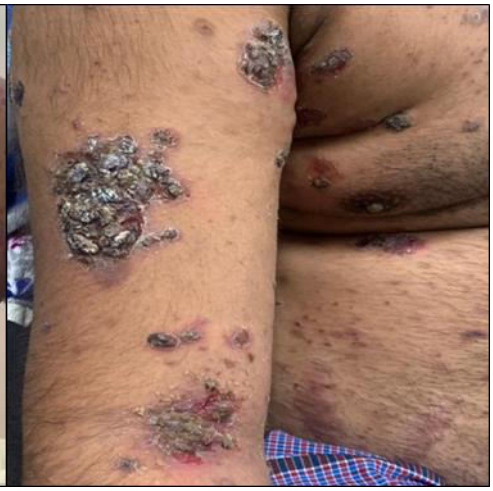

Fig. 4: Multiple Erythmatous erosion and crusting on upper limb

Fig5: After 5 Months of Retuximab therapy (Front)

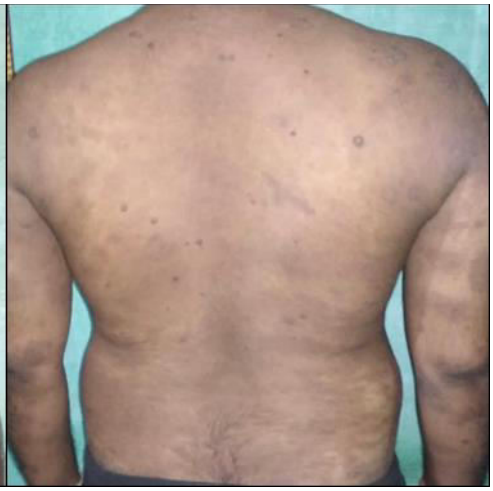

Fig6: After 5 Months of Retuximab therapy (Back)

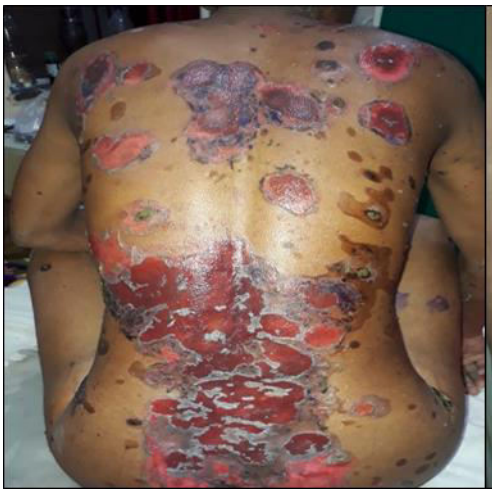

Fig7: Erosions over trunk

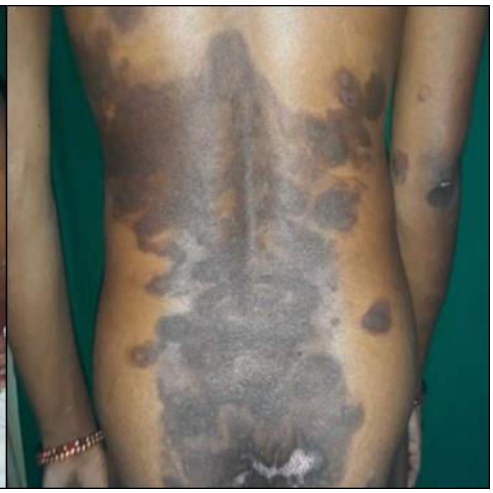

Fig8: After 4 months of helaed with hyperpigmentation

ADVERSE EFFECTS

Adverse effects, mostly mild, were seen in nine patients. The common adverse effects observed in our patients are enumerated in Table 2. An immediate infusion reaction, consisting of tachycardia, tachypnoea, nausea, and fever occurred in three (17.7%) patients at first exposure to rituximab. These were managed by slowing down the infusion rate. No

significant adjuvant drugs-related adverse effects were seen except for corticosteroid-related weight gain in three patients.

Table 2: Adverse effects

Adverse effect	No. of patients
Chills	6
Fatigue/weakness	5
Fever	3
Hypotension	3
Tachycardia	3
Tachypnea	3
Headache	2
Nausea	2
Pruritus	2
Oral candidiasis	1

DISCUSSION

The use of rituximab in pemphigus was first reported for the successful treatment of paraneoplastic pemphigus in a patient with follicular non-Hodgkin lymphoma. After that, various case reports and case series reported quite promising results of rituximab in pemphigus as well as pemphigoid patients not responding to standard therapy. Subsequently, multiple studies involving a larger number of patients established rituximab to be a durable, effective, and well-tolerated treatment for pemphigus as well as pemphigoid.[13-16]

Our study confirms the efficacy and safety of rituximab in pemphigus. Male preponderance has been seen in our study. In all of our patients, clinical improvement was noted in just over a month, and 86.3% of the patients achieved CR off therapy within 6.36 months following the second dose. Statistically, a significant reduction in the mean PAAS was seen six months after treatment. Relapse occurred in 14.3% of the patients who achieved complete remission after a mean duration of 15.5 ± 2.12 months. Comparable results have been reported from several recent studies. In a retrospective study by Sharma *et al*.,88% of the patients achieved complete remission after a mean duration of 4.36 months. Relapse occurred in 16% of the patients, and no significant severe adverse effects were seen.[15] In another retrospective study by Uzun*et al*.,96.2% of pemphigus vulgaris patients treated with rituximab achieved complete remission with or without adjuvant therapy, and rituximab use resulted in a significant reduction in steroid dosage during follow-up. In the same study, clinical relapse occurred in 44.4% of the patients after a mean duration of 13.1 ± 4.7 months.[16]

In the study by De D *et al*.,73.3% of the patients with pemphigus attained complete remission off treatment after a mean interval of 6.6 ± 3.4 months. Among these patients, 76.5% relapsed over a mean follow-up duration of 24.9 ± 17.1 months. No deaths and long-term complications occurred in this study.[17]

Early administration of rituximab in the treatment of pemphigus results in better outcomes, including a higher remission rate, a longer disease-free period, a lower rate of relapse, and a significant reduction in the requirement for corticosteroids and other immunosuppressants.[25] Among our study patients, fresh pemphigus patients (first-line group) required a shorter time to achieve CR on as well as off therapy, which led to fewer corticosteroids/immunosuppressant exposure and complications. None of these patients relapsed in the follow-up period.

The frequency of adverse reactions associated with rituximab as reported by previous studies, is quite variable. Serious adverse events (SAEs) including infusion reactions, have been reported to occur in 5.5-16% of patients. Our results were in line with those of earlier studies. Infusion reactions occurred in 17.7% of our patients. Fatal adverse effects have been reported to occur in 1.6-12.5% of the cases. However, we did not come across any fatal adverse event.

Various studies based on the use of rituximab in immunobullous disorders have reinforced the statement regarding rituximab acting like putting water on fire in pemphigus. [26] Despite the evidence of the efficacy of rituximab, many important questions remain unanswered. The number and timing of a rituximab course; the most effective protocol; whether rituximab should be a first-line agent for pemphigus patients, regardless of disease severity; and the duration of treatment all need to be ascertained. It is also important to know the critical predictors of disease relapse, as this information may determine the benefit of maintenance therapy. Thus far, information on the factors to indicate relapse remains sparse.

The main limitations of our study were the retrospective nature of the study, lack of comparison group, small sample size and unavailability of follow-up anti-desmoglein auto-antibodies levels and B cell markers.

CONCLUSION

Rituximab can be considered an important treatment option in patients with widespread recalcitrant or life-threatening PV. This drug has a good safety and tolerability profile and has shown a positive and long-

lasting response in patients with PV after a single course. These characteristics make it a therapy that is potentially able to modify the natural history of PV. Unfortunately, rituximab is very expensive, and its longterm effects are still unknown. Although its use is currently limited to selected cases of PV, controlled clinical trials with a greater number of patients are urgently needed.

FINANCIAL SUPPORT AND SPONSORSHIP
Nil.

CONFLICTS OF INTEREST
There are no conflicts of interest.

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