Original Research Article

Rituximab – An effective first line treatment in pemphigus vulgaris patients

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A B S T R A C T

Background: Rituximab is a humanized chimeric anti-CD20 monoclonal antibody that quickly lowers blood serum levels of anti-desmoglein autoantibodies, causing pemphigus lesions to heal.

Aims and Objective: To evaluate the efficacy of Rituximab in treating pemphigus vulgaris.

Materials and Methods: We identified and included 14 patients (3 males and 11 females), in the age group of 14 years to 67 years, of severe pemphigus vulgaris from 2016 to 2022 treated at our institution with rituximab infusion in our retrospective case study. Baseline anti-desmoglein antibodies 1 and 3 levels were elevated in all the patients. 12 of these patients received rituximab infusion as first-line treatment. 11(out of 14) patients received two doses of rituximab (1 gram in each) as intravenous infusions, as per the rheumatoid arthritis protocol; whereas, 3 (out of 14) received a single dose of intravenous rituximab infusion (1 gram). These patients were kept on maintenance dose of prednisolone/ mycophenolate mofetil post rituximab infusion.

Results: 14 patients of pemphigus vulgaris were enrolled in the study. The follow-up period ranged from 2 months to 6 years. All 14 patients responded well to therapy. No serious adverse events were observed. 10 (71.4%) of the 14 patients exhibited complete remission; whereas, 4 (28.6%) showed partial remission. Those with partial remission experienced relapse but the subsequent episode was less severe than the first episode. However, 2 patients who were non-responders to high doses of systemic steroids expired.

Conclusion: For treating patients with pemphigus vulgaris, rituximab infusion was found to be safe and effective. Hence, it should be considered as first-line for management of pemphigus vulgaris.

1. Introduction

Heizmann et al.[1] reported the first use of rituximab in the treatment of autoimmune bullous diseases, which included a successful case of paraneoplastic pemphigus. Rituximab has subsequently been used by numerous authors to treat a variety of immunobullous diseases, such as pemphigus vulgaris[2] and pemphigus foliaceus.[3]

Treatment of Pemphigus with rituximab leads to a rapid decline of anti-desmoglein serum auto-antibodies. In contrast, total IgG and the ratio of IgG to anti-microbial-recall antigens remain largely unchanged.[4–6]

Pemphigus is a rare group of autoimmune mucocutaneous blistering diseases that can be fatal. Autoantibodies against desmogleins, a type of epidermal adhesion protein is implicated in the pathogenesis of this disease. Rituximab (Reditux. Dr. Reddy's, Hyderabad, India and MabTheraTM, Roche, Basel, Switzerland), a monoclonal chimeric IgG1 antibody targeting the B cell-specific cell-surface antigen CD20, is one such newer novel therapy for pemphigus (an off-label indication for its use). It has so far been approved by the FDA for use only

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in CD 20+ B cell non-Hodgkin's lymphoma, treatment-resistant rheumatoid arthritis, Wegener's granulomatosis and microscopic polyangiitis). In many cases, especially in affluent patients, rituximab is now used as an off-label adjuvant therapy for paraneoplastic pemphigus, recalcitrant cases of pemphigus vulgaris or pemphigus foliaceous, and even as first-line therapy for newly diagnosed cases of pemphigus. administered as part of the rheumatoid arthritis (1000 mg twice, 15 days apart) or lymphoma (375 mg/m2 body surface area weekly, for 4 weeks) protocols; smaller doses (500 mg twice, 15 days apart) have also been found to be effective.[7]

Pemphigus vulgaris (PV) is the main subtype of the pemphigus group with potentially fatal outcomes mediated by autoantibodies against desmoglein 1 (Dsg. 1) and desmoglein 3 (Dsg. 3), adhering molecules of the epidermal and external mucosa, respectively.[8]

PV is usually fatal without proper treatment. There is variation in the epidemiology and natural course of the disease across different nations, with notable differences in the incidence and age distribution. Pemphigus is comparatively common[7,9] with significant interstate variation in India. The most prevalent subtype, PV, accounts for 75–92% of all pemphigus patients.[10] Immunosuppressive agents such as cyclophosphamide, methotrexate, cyclosporine, mycophenolate mofetil and azathioprine are used in pemphigus for their steroid-sparing effect. Rituximab is a chimeric monoclonal antibody that targets the CD20 molecule on B-cells.[11]

The comparatively elevated expense of rituximab in India in contrast to conventional options restricts the extensive application of this treatment modality, despite its favorable outcomes in treating resistant illnesses and potentially fatal cases of pemphigus.[12]

In the following situations, stopping rituximab therapy is recommended:

1. Serious infections.
2. Major side effects, like an allergic reaction in individuals who are intolerant to mouse proteins.
3. Pregnancy.[13]

We report clinical experience from a single institution in a series of 14 patients with PV. Of these patients with PV, 2 were refractory to CS and ultimately required rituximab infusion. 12 patients received rituximab infusion as first-line treatment. 11 (out of 14) patients received two doses of intravenous rituximab (1 gram in each), following the rheumatoid arthritis protocol; whereas 3 patients received a single dose of intravenous rituximab infusion (1 gram).

2. Materials and Methods

The retrospective study was conducted in the department of Dermatology, in Dr. D.Y. Patil Hospital, Navi Mumbai involving 3 males and 11 females in the age group of 14-67 years with pemphigus (fresh, relapse, and recalcitrant cases) who received rituximab infusion from 2016 to 2022. All patients had been diagnosed with PV by clinical, histopathological and immunofluorescence features. Permission from the Institutional Ethical Committee was taken for conducting the study. For each case, data regarding age, sex, duration of disease, presence of cutaneous and/or mucosal involvement, history of any previous treatment taken, were analysed. Baseline anti-desmoglein 1 and 3 levels were documented for each patient which were elevated. 12 of these patients received rituximab infusion as first-line treatment; whereas, 2 of them were non-responders to oral steroids and received rituximab infusion as the second line of treatment.

As premedication, patients were given hydrocortisone 100mg intravenously, paracetamol 1gm stat intravenously and pheniramine maleate 2cc stat intravenously, sequentially on the day of infusion. After 30 minutes of these premedication, rituximab (1 g) intravenously in 400 ml of normal saline was given slowly over 6 to 8 hours.

Patients were closely monitored for any adverse effects. The patients were followed up every month for the first 6 months and later on followed up once in every 6 months. Patients were kept on a maintenance dose of low-dose prednisolone or mycophenolate mofetil.

3. Results

Table 1: Demographic characteristics (n=14)

Characteristic	Value
Age Range	14-67 years
Male	3 (21.4%)
Female	11 (78.6%)

Table 1 shows that 11 (78.6%) women and 3 (21.4%) males were in the age range of 14–67 years.

Table 2 shows that all the patients developed both cutaneous and mucosal lesions. 12 (85.7%) received rituximab infusion as the first line therapy whereas 2 (14.3%) received it as the second line of management on failure of systemic corticosteroid.

Table 2 shows that 11 (78.6%) patients received two doses of rituximab (1 gram in each) as intravenous infusions, as per the rheumatoid arthritis protocol; whereas, 3 (21.4%) received a single dose of intravenous rituximab infusion (1 gram).

Table 2 shows that all 14 patients responded to therapy. The patients tolerated Rituximab well and no grievous adverse events were observed. 10 (71.4%) out of the 14 patients showed complete remission (the absence of new or established lesions); whereas, 4 (28.6%) showed partial remission (the presence of transient new lesions that heal within a few weeks). Those with partial remission

Table 2:

	No. of cases	Percent
Therapy		
First line (Rituximab Infusion)	12	85.7
Second Line Management	2	14.3
Doses		
Single course of rituximab, two doses of rituximab (1 gram in each)	11	78.6
Single dose of intravenous rituximab infusion (1 gram)	3	21.4
Therapy Response		
Complete Remission (the absence of new or established lesions)	10	71.4
Partial remission (the presence of transient new lesions that heal within few week)	4	28.6
Death		
During Follow up Period	2	14.28
After the infusion (due to unexplained reasons)	1	7.14
Due to perforation peritonitis	1	7.14

experienced relapse but the subsequent episode was less severe than the first episode. All the patients were maintained on adjuvant therapy with either low-dose prednisolone or mycophenolate mofetil.

Table 2 shows that 2 of the 14 patients died during the follow-up period. 1 died a year after the infusion due to unexplained reasons and 1 died due to perforation peritonitis, 3 months following the infusion.

4. Discussion

4.1. First-line vs. Second-line treatment

The majority of patients in this case series (12 out of 14) received rituximab infusion as a first-line treatment. This reflects the growing confidence among clinicians in rituximab's efficacy and safety as an initial therapeutic option for pemphigus vulgaris. The decision to employ rituximab as a first-line treatment aligns with recent studies and expert recommendations, which advocate for its use due to its potential to induce rapid remission and reduce the need for prolonged corticosteroid exposure.[5,6] Importantly, in cases where oral steroids failed to control the disease (2 out of 14 patients), rituximab was used as a second-line treatment, emphasizing its role as a valuable alternative for non-responders.

4.2. Clinical response and remission rates

The observation that 10 (71.4%) out of 14 patients achieved complete remission with rituximab is a significant finding. Complete remission implies not only the control of active lesions but also a reduction in the requirement for systemic corticosteroids, which have their own set of adverse effects.

However, it is important to note that 4 patients (28.6%) achieved partial remission. Similarly in the study of Sharma VK et al. (2016)[13] in 22 cases (88%) there was a complete remission. Three patients (12%) had a partial response, one of whom also had vitiligo vulgaris and persistent plaque psoriasis.

4.3. Safety and tolerability

An important aspect of this study is the safety and tolerability of rituximab in pemphigus vulgaris patients. The absence of any serious adverse events, especially in a condition where patients are often exposed to prolonged corticosteroid therapy with its associated side effects, highlights the favorable safety profile of rituximab. The absence of life-threatening complications during the infusion and follow-up period is reassuring for clinicians and patients alike. Also, in the study of Kanwar AJ et al. (2012)[7] seven patients showed good tolerability of the medication with no adverse effects; however, two patients experienced angioedema as an acute complication in the second hour of infusion, requiring stopping the infusion in one patient.[14]

4.4. Mortality and causes

The report of two patient deaths during the follow-up period merits consideration. The first patient's unexplained death a year after rituximab infusion raises questions about the possibility of long-term adverse effects that require further investigation. The second patient's death due to perforation peritonitis, occurring 3 months following rituximab infusion, underscores the importance of monitoring patients for unexpected complications, especially in the context of immunosuppressive therapies. Similarly in the study of Kanwar AJ et al. (2006)[15] in 14 (4%) of the patients, pemphigus-related death occurred.

5. Conclusion

In conclusion, the findings from this retrospective case series suggest that rituximab holds promise as an effective and safe treatment option for pemphigus vulgaris. The data emphasize the potential benefits of using rituximab as a first-line treatment, its ability to induce complete remission or mitigate disease severity, and its overall tolerability.

However, the report of patient deaths underlines the necessity for continued surveillance and careful monitoring of patients receiving rituximab.

Additional research, such as randomized controlled trials, is necessary to confirm these results and offer a more thorough comprehension of rituximab's function in the treatment of pemphigus vulgaris.

6. Source of Funding

None.

7. Conflict of Interest

None.

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