Rituximab in Pemphigus – An Observational Study from a Tertiary Care Center of North India

Abstract

Background: Pemphigus is a group of potentially fatal autoimmune mucocutaneous blistering diseases. Rituximab (RTX) is a chimeric anti-CD20 (anti-cluster of differentiate 20) monoclonal antibody being increasingly used and becoming the first-line therapy in the management of pemphigus. Aims and Objectives: This was an observational study 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. Materials and Methods: The study included pemphigus patients coming to our immunobullous clinic who did not respond to conventional therapy or relapsed after receiving conventional therapy as well as fresh cases between January 2019 and October 2021. 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: Sixteen (ten males and six 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 15 (93.75%) patients with PV (14 mucocutaneous type and 01 mucosal) and one (6.25%) with pemphigus foliaceus. Among these patients, nine (56.25%) were relapse cases, four (25%) were non-responders, and three (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 (ranging from 18 weeks to 35 weeks). Rituximab was well-tolerated by our patients, and no serious adverse events were observed. The main limitation of our study was the small sample size and the lack of a comparison group. Conclusion: Rituximab is a safe and effective treatment for pemphigus.

Keywords: Autoimmune, foliaceus, pemphigus, rituximab, vulgaris

Introduction

Pemphigus and pemphigoid are autoimmune bullous skin diseases that are caused by autoantibodies against adhesion molecules of the epidermal and dermo-epidermal junction respectively.[1,2] These diseases may be associated with a severe and potentially fatal course and may require long-term systemic treatment with high dose corticosteroids and other steroid-sparing immunosuppressive drugs, such as azathioprine, mycophenolate mofetil (MMF), or cyclophosphamide. These treatment modalities can lead to serious adverse effects, require careful monitoring, and may not be effective in all patients.[3]

Rituximab, a chimeric murine/human monoclonal antibody directed against the cluster of differentiate 20 (CD20) antigen on B lymphocytes, is a major therapeutic agent in the management of several B-cell malignancies and because of its B-cell-depleting effect it has been found to be effective in treating various autoimmune conditions in which autoantibodies are thought to play a pathogenetic role.[4,5] Rituximab is believed to act via different mechanisms responsible for B-cell depletion, such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity, and direct triggering of apoptosis.[6] The antibody is neither internalized by the B-cell nor shed from the plasma membrane, contributing to its persistence on the cell surface.[7]

Rituximab was used for the first time in the treatment of autoimmune bullous diseases by Heizmann et al.,[8] who reported a case of paraneoplastic pemphigus successfully treated by rituximab. Though initially

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Access this article online
Website: www.idoj.in
DOI: 10.4103/idoj.idoj_170_22
Quick Response Code:

How to cite this article: Hassan I, Rehman F, Sultan SJ, Aslam A, Tasaduq I, Reyaz S. Rituximab in pemphigus – An observational study from a tertiary care centre of North India. Indian Dermatol Online J 2022;13:620-4.

Received: 20-Mar-2022. Revised: 16-May-2022. Accepted: 29-May-2022. Published: 05-Sep-2022.
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 nowadays recommended as first-line treatment, especially for the treatment of naïve pemphigus patients.[9,10]

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.[11] With this study, we also intended to present our experience with fixed-dose rituximab therapy in pemphigus from a tertiary care hospital in North India.

**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 October 2021. Approval was sought from the institutional ethics committee, and written informed consent was obtained from each patient.

Diagnosis of pemphigus was made based on Tzanck smear, histopathology, and 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, sepsis, and viral hepatitis); and (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 (methylprednisolone, 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, the adjuvant treatment was gradually tapered with an expectation to discontinue all adjuvant drugs at complete clinical remission or at six months after the second dose. Response to treatment was determined according to the definitions of an international consensus statement.[12]

**Statistical analysis**

The statistical analysis was performed using the Statistical Package of Social Sciences (SPSS) software version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as measures of central tendency, and categorical variables were presented as absolute numbers and percentages.

**Results**

Sixteen patients were included in the study comprising ten (62.5%) males and six (37.5%) females. The age of these patients ranged from 27 to 60 years, with a mean of 43.8 ± 9.8 years. There were 15 (93.75%) patients with pemphigus vulgaris (PV) (14 mucocutaneous type and 01 mucosal) and 1 (6.25%) with pemphigus foliaceus. Among these patients, nine (56.25%) were relapse cases, four (25%) were non-responders, and 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. Twelve (75%) 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). Fourteen (87.5%) patients reached complete remission (CR) off therapy over a median time of 6.36 months (ranging from 18 weeks to 35 weeks) [Figures 1–3]. Two (12.5%) 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 = 14), relapse occurred in two (14.3%) patients at 14 and 17 months, respectively (mean 15.5 ± 2.12 months). These two patients received a second cycle of rituximab therapy, and both of them are currently in partial remission while on therapy (prednisolone/azathioprine).
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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, tachypnea, nausea, and vomiting 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.

Discussion

The use of rituximab in pemphigus was first reported by Heizmann M et al.,[8] (2001) with 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. In all of our patients, clinical improvement was noted in just over a month, and 87.5% 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.,[14] 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. In another retrospective study by Uzun et al.,[15] 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.

In another retrospective study by Sharma et al.,[16] 80.33% of the patients achieved complete remission off adjuvant

| Table 1: Patient characteristics |
|---------------------------------|
| Total Number of patients=16     |
| Characteristics of pemphigus patients |
| Gender                         |
| Male                           | 10 (62.5%) |
| Female                         | 6 (37.5%)  |
| Age [Mean, (Range)]            | 43.8±9.8 (27 to 60 years) |
| Diagnosis                      |
| Pemphigus vulgaris             | 15 (93.75%) |
| Mucocutaneous                  | 14 (93.3%) |
| Mucosal only                   | 01 (6.7%)  |
| Pemphigus foliaceus            | 1 (6.25%)  |
| Baseline PAAS [mean, (range)]  | 15.7±6.7 (6.7 to 28.8) |
| Underlying disease             |
| Hypertension                   | 2          |
| Diabetes mellitus              | 2          |
| Rheumatoid arthritis           | 1          |
| Dyslipidemia                   | 1          |
| Disease duration before        | 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)| 13 (81.25%) |
| PAAS 6 months post rituximab [mean, (range)] | 1.7±1.5 (0 to 4.2) |

| 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          | 2               |
| Paronychia                | 2               |
| Herpes zoster             | 1               |
| Herpes simplex            | 1               |

Figure 1: a) Face and trunk lesions, and b) Scalp lesions in a patient of pemphigus vulgaris before treatment. c and d) showing complete resolution of lesions in the same patient, seven months after treatment.
therapy after a mean duration of 8.08 ± 4.45 months while 27.9% of the patients relapsed after a mean duration of 23.94 ± 13.15 months. In the study by De D et al,[17] 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.[18,19] 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.[17,20] 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.[20] However, we did not come across any fatal adverse event.

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

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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