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Original Research Article

Post biologic scenario in pemphigus patients at a tertiary care institution

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ABSTRACT

Background: Rituximab is increasingly used for the treatment of pemphigus. Data derived from single center studies following a uniform treatment protocol are limited. The effect of demography and disease type on treatment response is poorly characterized. Aim of this study was to assess the efficacy, adverse effects of rituximab, adjuvants and follow up in pemphigus patients.
Methods: Author undertook a retrospective review of records of 26 pemphigus patients (pemphigus vulgaris 25 and pemphigus foliaceus 1) who had received rituximab infusion. Oral prednisolone was administered in doses up to 0.5 mg/kg of body weight after infusion and tapered over the next 3-4 months according to the disease activity. However, other immunosuppressive agents such as cyclophosphamide and AZT were continued for one year after clinical remission was achieved.
Results: Complete remission was observed in 23 (88.5%) patients. The mean time to disease control and complete remission was 1.10 and 4.36 months, respectively. Three patients experienced relapse after a mean duration of 26 months. Infectious complications like candidiasis and furunculosis developed in two patients. Two patients had hypotension during infusion.
Conclusions: Rituximab is an effective agent in the treatment of pemphigus and also for a long duration of remission with a lower initial dose of oral prednisolone. Severe side effects were rare.

Keywords: Adjuvants, Follow-up, Pemphigus, Rituximab

INTRODUCTION

Pemphigus is a group of rare, potentially fatal, autoimmune mucocutaneous blistering diseases with autoantibodies against epidermal adhesion proteins known as desmoglein. Pemphigus vulgaris (PV) is typically associated with autoantibodies to desmoglein 3 in mucosal dominant disease and to desmoglein 3 and desmoglein1 in mucocutaneous disease.[1] Systemic corticosteroids are still the most effective therapeutic agent for pemphigus.[2] 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 but has no action on CD20 negative early pre B cells and terminally differentiated plasma cells.[3] It is a US Food and Drug Administration approved drug for lymphoma, rheumatoid arthritis, chronic lymphocytic leukemia and Wegener's granulomatosis but has also been used off-label in severe and refractory pemphigus since 2002.[4] In June of 2018, the U.S. Food and Drug Administration (FDA) approved rituximab for the treatment of adults with moderate to severe PV.[5]

The objective of this retrospective study was to assess the efficacy, adverse effects of rituximab, adjuvants and follow up in the treatment of pemphigus patients, most of whom were refractory to conventional therapy.

METHODS

The records of the 26 patients with pemphigus was reviewed who were treated with rituximab infusion in the department from June 2016 to July 2019. Of those, twenty patients were recalcitrant to prior dexamethasone cyclophosphamide pulse therapy (DCP) and rituximab was used as first-line therapy in six patients. Skin biopsy, Tzanck smear and direct immunofluorescence were done at baseline. A Mantoux test, echocardiogram, viral markers for hepatitis B surface antigen, anti-hepatitis C virus, Enzyme-Linked Immunosorbent Assay (ELISA) for human immunodeficiency virus and routine biochemical investigations were also performed. After premedication (100 mg of hydrocortisone intravenously, 22.75 mg of pheniramine maleate intravenously and 500 mg of paracetamol orally), rituximab infusion was given under strict monitoring over 5-6 hours. The rate of infusion was initially 50 ml/hour, escalated by 50 ml/hour every 30 min upto a maximum infusion rate of 400 ml/hour. Twenty-six patients received two doses of 1 gm of rituximab, 2 weeks apart. Oral prednisolone was administered at a dosage up to 0.5 mg/kg of body weight and tapered over the next 3-4 months according to the disease activity. However, other immunosuppressive agents such as cyclophosphamide or azathioprine were added for one year after clinical remission. Prophylactically, dapsone was co-administered to overcome Pneumocystis carinii in all cases.

The early endpoint was time to disease control which was defined as the time at which new lesions ceased to form and established lesions began to heal. Among the late endpoints, complete remission (CR) was defined as the absence of new or established lesions for at least 2 months. Partial remission (PR) was defined by the presence of transient new lesions that healed within 1 week with or without minimal therapy, including topical steroids. Relapse was characterized by the appearance of 3 or more new lesions in a month that did not heal spontaneously within 1 week or by the extension of established lesions, in a patient who had achieved disease control.

RESULTS

There were 26 patients with pemphigus comprising 8 men 17 women and one pediatric (Figure 1) with a mean age of 37.15(12-59) (Figure 2); the duration of disease ranged from 7 months to 3 years (mean duration:15.16 months).

In all cases, both skin and mucosa were involved. Based on the histological and immunofluorescence findings, the diagnosis of pemphigus vulgaris was made in 25 patients, and pemphigus foliaceus in one. The follow-up period after the last rituximab infusion ranged from 7 to 36 months (mean: 17.51 months). CR was seen in 23 (88.5%) out of 26 patients. A partial response was noted in 3 (11.5%) patients (Figure 3).

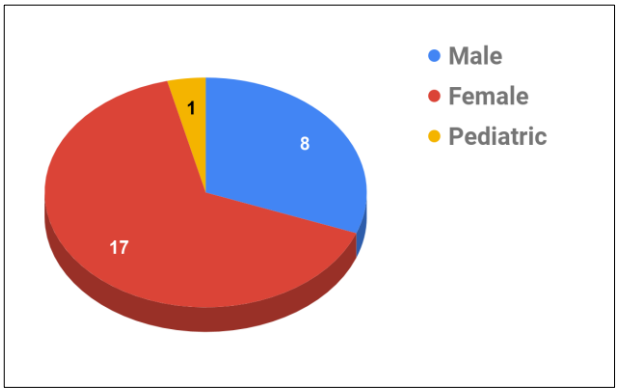

Figure 1: The proportion of male, female and pediatric cases.

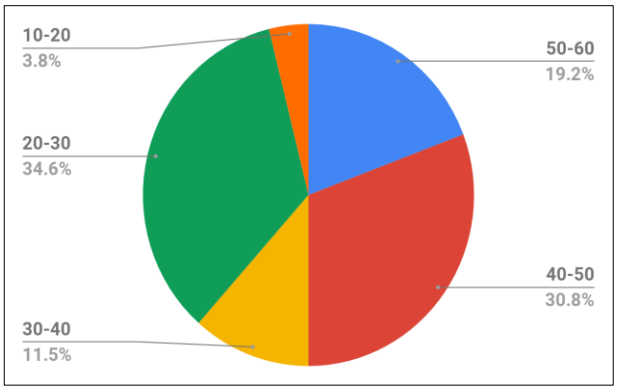

Figure 2: Distribution among various age groups.

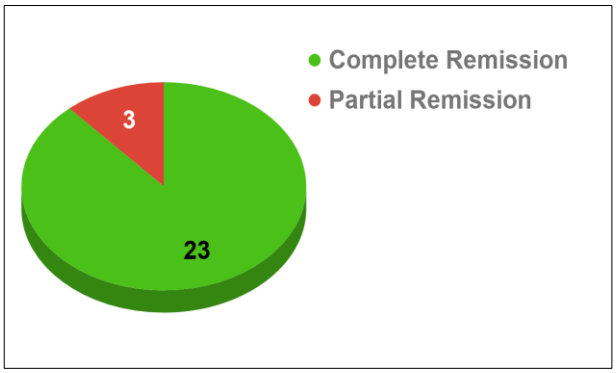

Figure 3: The proportion of CR and PR.

The mean time to disease control was 1.10 months and time to CR was 4.36 months. Twenty patients had already received several cycles of monthly dexamethasone or dexamethasone cyclophosphamide pulse therapy (range: 12-72, mean: 19.8 cycles). Three (11.5%) patients experienced relapse one at 14th month, one at 28th month

and one at 36 months. Two patients developed hypotension during rituximab infusion which was corrected by slowing the infusion; two patients developed an infection after rituximab infusion (oral candidiasis-1; furunculosis-1) but resolved with antifungals and antibiotics respectively. Out of the 26 patients, 3 were reactive to hepatitis B and 2 reactive to Hepatitis C and were on antiviral drugs (Figure 4).

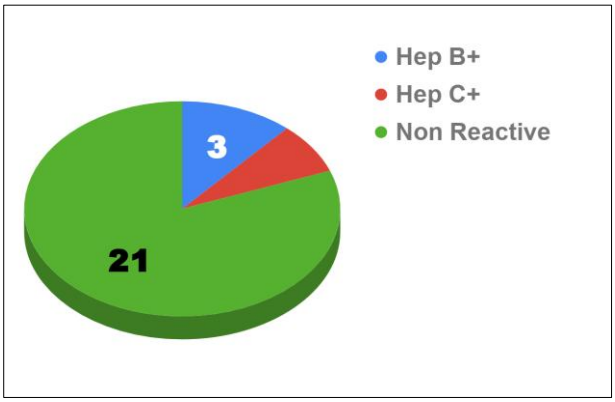

Figure 4: The proportion of hepatitis B and hepatitis C infection.

Among the cases studied, one belongs to the pediatric group, Juvenile PV, a 12-year-old male child who was put on 500 mg rituximab on day 1 and day 15. He developed oral candidiasis which resolved with appropriate treatment.

DISCUSSION

Pemphigus is a group of autoimmune blistering disorders, clinically characterized by mucocutaneous blisters and erosions, histopathologically by intraepidermal acantholysis, due to autoantibodies directed against the cell surface proteins, desmoglein and associated with high mortality and morbidity. However, the advent of corticosteroids dramatically changed the outlook of this invariably fatal disease and reduced the mortality rate to <10%.[6] Another milestone in the therapeutics of pemphigus in India was the use of dexamethasone cyclophosphamide pulse (DCP) therapy by Pasricha and Ramji in 1984. Since then, DCP and oral corticosteroids have been the backbone of pemphigus treatment in India.[7] However, long-term corticosteroid intake is associated with various metabolic complications, global immunosuppression, and an antecedent risk of serious infections.

The next major development in pemphigus treatment was the use of rituximab in 2001 by Heizmann et al.[4] This serendipitous discovery of improvement in mucocutaneous lesions of paraneoplastic pemphigus when rituximab was used to treat non-Hodgkin's lymphoma dawned upon a new era of targeted therapy to treat autoimmune blistering diseases. Rituximab, a chimeric monoclonal antibody, selectively acts on the CD20 expressing B cells, which are known to secrete autoantibodies targeting the epidermal desmoglein, causing direct induction of apoptosis, complement-dependent cytotoxicity (CMC), and antibody-dependent cellular cytotoxicity (ADCC). In the Indian scenario, rituximab was first used by Kanwar and colleagues in 2010 and the promising findings were first published in 2012.[8] The usage of rituximab has increased many folds over the recent years with the availability of rituximab biosimilars, which show similar efficiency as the reference molecule.[9]

Rituximab has been used in various protocols and in combination with other immunomodulators in the treatment of pemphigus. Currently, the two commonly used protocols in India are the Lymphoma Protocol (LP) and rheumatoid arthritis (RA) protocol. Kanwar et al. treated 10 pemphigus patients by RA protocol. At a mean follow-up of 33.4 weeks, three patients had achieved CRoff all treatment [CR (off)] and four patients had achieved CRon minimal therapy [CR (on)]. One patient died of sepsis. In this study, the mean time to disease control (TDC) was 8 weeks. In a retrospective review, Sharma et al, reported the treatment outcome of 25 pemphigus patients treated with rituximab mostly by RA protocol.[10] At a mean follow-up of 18 months, CR was noted in 22 patients and PR in 3 patients with a mean TDC of 5 weeks. Relapse was seen in four patients after a mean duration of 11.75 months. Adverse events included disease exacerbation in two patients, acute respiratory distress syndrome and cellulitis in one patient each. Study correlates with the results of Sharma et al. The treatment outcome of 26 patients after a mean duration of 15.16 months have been reported among whom CR was noted in 23 patients and PR in 3 patients and relapse was noted in 3 patients. Londhe et al, treated 24 pemphigus patients with a modified version of LP.[11] At a mean follow-up of 18 months, all 24 patients had responded to treatment with 9 patients achieving CR (off), 10 achieving CR (on), and 5 patients achieving a PR. Adverse effects were limited to infusion reactions. The adverse effects among patients include hypotension in 2 patients and infection in 2 patients. Thus, study also correlates with the results of Londhe et al. In a follow-up publication of this cohort Khopkar and colleagues reported the outcome of 114 pemphigus patients (including the 24 cases reported by the authors in 2014) receiving rituximab.[12] Forty-nine (43%) cases had achieved CR (off), 32(28%) patients had achieved CR (on), and 12 patients had achieved PR at the end of 24 months. Relapse was noted in 13(11.4%) patients. There was no remarkable difference in the clinical outcome between the patients treated with RA protocol (n=66) and LP (n=48). In the systematic analysis of published literature by Ahmed and Shetty, the authors found CR in a statistically higher number of patients receiving RA protocol.[13] Also, patients receiving RA protocol were more likely to be off all treatment during post-treatment follow-up. These findings by Ahmed and Shetty correlates with this study also.

The common variation in the RA protocol was the high- and low-dose rituximab administration. The high-dose regimen involved administration of two doses of 1000 mg of rituximab 2 weeks apart. Whereas, in the low-dose regimen, two doses of 500 mg rituximab were administered 2 weeks apart. In a randomized control trial, Kanwar et al, compared the clinical and immunological outcomes of pemphigus patients treated with high- and low-dose RA protocol.[14] The clinical response as evidenced by the fall in the disease severity scale was significantly more in the high-dose group. Additionally, the immunological parameters assessed by fall in the anti-desmoglein antibody titer and B cell repopulation was significantly better in patients receiving the high-dose regimen. The meta-analysis of low- and high-dose regimen by Wang and colleagues also reported longer duration of CR with high-dose regimen.[15]

In a retrospective review of patient records, Vinay et al, reported the encouraging results of rituximab treatment (two doses of 500 mg 15 days apart) in childhood and juvenile pemphigus patients.[16] CR (off) treatment was achieved in 7/10 patients at a median follow-up period of 16 months. Relapse was seen in six patients by a mean of 13 months, which showed good treatment response to repeat infusions of rituximab and/or conventional immunosuppressants. Author have also reported the encouraging results of rituximab treatment (two doses of 500 mg 15 days apart) in one case of juvenile pemphigus. CR (off) was achieved in a follow-up period of 9 months. Except the occurrence of oral candidiasis in this patient, which was managed with systemic fluconazole and well responded by the patient, no other adverse effects noted in this patient. Oral lesions of pemphigus show treatment refractoriness in comparison to cutaneous lesions.[17] Vinay et al, treated three pemphigus patients with refractory oral ulcers using intralesional rituximab (5 mg/cm^2 two injections 15 days apart) with a good response in all.[18] Rituximab has also been used in special situations in treating paraneoplastic pemphigus and in pemphigus patients with hepatitis B and C infection.[19] who treated 3 patients. Author have also infused Rituximab in Hepatitis B (3 cases) and Hepatitis C (2 cases) infection patients undercover of antivirals and the patients are under regular follow-up. Author haven't come across any adverse effects among those patients with hepatitis infection. Author are the first to use Rituximab in the maximum number of Pemphigus Vulgaris patients with Hepatitis infection in the Indian scenario

Various studies have analyzed the immunological changes after rituximab treatment. Post-rituximab treatment, a gradual fall in anti-desmoglein antibody titers is generally observed. In the study by Kanwar et al, the clinical response paralleled the fall in anti-desmoglein 1 antibody indices, whereas there was only a partial reduction in anti-desmoglein 3 titers. The fall in CD19 cell count is dramatic after rituximab infusion and is seen as early as 2 weeks. Even low-dose RA protocol and intralesional rituximab injection successfully reduced CD19 cell count. However, CD19 cell repopulation is earlier in patients receiving low-dose rituximab regimens compared to patients receiving high-dose regimen. Since relapses are associated with B cell repopulation, low-dose regimens may have a higher relapse rate compared to high-dose regimens.[20] Bhattacharjee et al, studied the effect of rituximab on circulating T regulatory cells in 18 pemphigus patients.[21] No direct relationship was found between the disease severity/clinical response and circulating T regulatory cells. In the seminal study by Colliou et al, increased CD19+CD27 - naïve B cells to CD19+CD27+ memory B cells ratio, increased transitional B cells and interleukin-10 - secreting regulatory B cells were associated with complete remission.[22] Delayed appearance of memory B cells and the disappearance of desmoglein-specific circulating immunoglobulin G-positive (IgG+) B-lymphocytes were also associated with long-lasting remission with rituximab.

Under the global scenario, in a landmark randomized controlled trial, Joly and colleagues compared the clinical outcome of patients receiving rituximab and low-dose corticosteroids compared to corticosteroids alone.[23] The study recruited 91 treatment naïve pemphigus patients and randomized them in 1:1 ratio to rituximab or corticosteroid group. At the end of 36 months of follow-up, 41/46(86%) of patients in the rituximab arm were in CR compared to 15/44(34%) patients in prednisolone only arm. The adverse effects were common and more severe in the prednisolone only group.

The noted deviation by Joly et al, was the use of rituximab as a first line adjuvant in treatment naïve patients. Though many authors have previously suggested using rituximab as a first line adjuvant, most of the current treatment guidelines recommend rituximab as a second or third line drug after failing conventional immunosuppressants.[24] The trial by Joly et al, has paved the way for considering rituximab treatment earlier in the disease course. Using rituximab early in the disease course has added advantage. Cho et al, suggested that relapse after rituximab treatment was associated with prior long-term use of conventional immunosuppressive agents.[25] Also, the probability of achieving CR (off) is more in pemphigus patients receiving rituximab within 6 months of disease onset.[26] The United States Food and Drug Administration has now approved rituximab for the treatment of adults with moderate-to-severe pemphigus vulgaris, which makes the drug the first biologic approved for the treatment of pemphigus vulgaris. The most recent guidelines by the international panel of experts recommend rituximab as a first line treatment option for pemphigus.[27]

Though rituximab has now been firmly established as a treatment modality of pemphigus, many questions still remain unanswered. Important among these is the indication to use rituximab. Should rituximab be the first

line therapy for all pemphigus patients irrespective of disease severity or disease duration? Should rituximab treatment be guided by immunological parameters like desmoglein indices, CD19, and CD4 cell counts? Is there a subset of patients who benefit from starting rituximab early in the disease course? Future studies are required to answer these questions for a patient-tailored treatment approach.

Rituximab is generally used in combination with low-dose corticosteroids. Ahmed and colleagues strongly advocate using IVIg in combination with rituximab.[28] Few authors have used azathioprine, cyclophosphamide, and mycophenolate mofetil as adjuvants in addition to rituximab. However, there is no consensus on the use of other immunosuppressants and immunomodulators along with rituximab. Questions regarding optimal dose, frequency, total number of maintenance infusions to use, and treatment schedule for relapses also needs to be answered.

The literature on vaccination for patients receiving rituximab is blurred. Live vaccines such as influenza and varicella-zoster vaccine are contraindicated while on immunosuppression.[29] Whereas killed vaccines, subunit vaccine, and other non-live inactivated vaccines can be safely administered. The literature-based immunization recommendations for immunosuppressed autoimmune bullous dermatoses patients recommend vaccination with non-live vaccines of pneumococcal, hepatitis B, and inactivated influenza vaccine (annually).[30] The same can be currently followed for patients receiving rituximab; however, specific data on immune conversion and complications after vaccination are required.

Regarding Rituximab for maintenance therapy, though many long-term case series and a few randomized control trials have now clearly established the efficacy of rituximab to induce remission. there are studies and systematic analysis which consistently reports a relapse rate of 40-60%. Interestingly, in their randomized control trial, Joly et al, administered 500 mg rituximab at 12 and 18 months irrespective of the disease activity. This was based on the author's observation that the desmoglein indices increase 12 months after rituximab infusion following the initial fall in its titers. It is also supplemented by the observation that the CD19 repopulation and relapses are common after 12 months and usually occur at a median of 15 months. Therefore, few authors recommend additional rituximab infusions every 6 monthly to maintain clinical remission.[31] A previous study by Gregoriou et al, found no additional benefit from prophylactic infusions of rituximab.[32] However, many recent studies have reported low or no relapse rate with maintenance rituximab infusions. However, there is uncertainty on the optimal dose (500 mg or 1 g) to be used and frequency of administration (every 6 months or 1 year) when used for maintenance therapy. Many immunologic markers can be used to predict disease relapse including desmoglein indices, CD19, and CD4 cell counts. Future studies are needed to assess these markers as criteria to administer or withdraw rituximab maintenance.

Regarding Ultra low-dose Rtx, it acts by depletion of CD20 expressing circulating B cells but has no action on CD20 negative early pre-B cells and terminally differentiated plasma cells.[33] The B cell burden in autoimmune blistering diseases is much lower than in lymphoproliferative diseases. Recent studies have found 97% of circulating B cell depletion with rituximab dose as little as 1 mg/m^2 (contrasting to 375 mg/m^2 in lymphoma).[34] Previously similar findings was reported with intralesional injection of ultra-low-dose rituximab injection (30-40 mg) wherein CD19 B cell suppression was seen within 2 weeks. There has been a suggestion that 100 mg rituximab may be sufficient to induce depletion of B cells for 3 months and, consequently, two doses of 100 mg every 3 months could deplete the B cell population for 6 months.[35] However, well-designed clinical trials are warranted to determine its efficacy in the context of treating autoimmune blistering disorders.

Regarding future strategies beyond rituximab, use of newer generation anti-CD20 monoclonal antibodies is being explored to treat B cell mediated diseases including pemphigus.[36] Anti-CD20 antibodies are categorized into Type I (including rituximab, ofatumumab, veltuzumab, and ocrelizumab) and Type II (including tositumomab or obinutuzumab), depending on the mechanism of action.[37] Type I antibodies cause clustering of CD20 that enhances the recruitment and activation of complement for a potent CDC response. On the other hand, Type II antibodies exhibit stronger homotypic adhesion and induction of direct cell death but with a minimal CDC response. The newer generation anti-CD20 monoclonal antibodies have added advantage.[38] Humanized monoclonal antibodies are less immunogenic than mouse-derived proteins. Few of these antibodies can be injected subcutaneously, obviating the need for hospitalization for intravenous infusions. Increased binding to the affinity effector cells leads to increased B cell depletion, which may translate to better/prolonged clinical efficacy. Veltuzumab, a second-generation Type 1 anti-CD20 antibody has been reported useful in inducing remission in a treatment resistant case of pemphigus.[39] Phase III studies are currently being conducted for ofatumumab and anti-BAFF antibodies in pemphigus patients. Monoclonal antibodies targeting CD19 and CD22 are being explored in multiple sclerosis and systemic lupus erythematosus, which may in future be evaluated in treating autoimmune blistering diseases. Another interesting strategy is the antigen-specific B cell depletion using Chimeric Autoantibody Receptor (CAAR) T cells. In this strategy, biochemically engineered T cells specifically recognize and deplete anti-desmoglein 1 and anti-desmoglein 3 secreting B cells.[40] CAAR T cells have the ability to proliferate and expand in vivo, which may lead to long-lasting effects.

The major limitation of the study was the small sample size, retrospective nature of the study, lack of a validated severity score, unavailability of follow-up anti-desmoglein auto-antibodies levels and B cell markers.

CONCLUSION

Rituximab is an effective form of therapy for pemphigus. It was found useful in long-standing as well as early disease, juvenile pemphigus patient and among patients with hepatitis B and hepatitis C infection. Severe side effects are rare but careful monitoring should be done in all patients to avoid complications. Further larger studies and randomized controlled trials would be valuable to determine the safety and efficacy of this drug as a first-line agent in pemphigus. In view of immunological marker, like desmoglein indices, CD19 and CD4 cell counts, which can be used to predict disease relapse, as a criterion to administer or withdraw rituximab maintenance are beyond scope due to financial constraints. The current treatment options, according to the British Association of Dermatologists guidelines, for Pemphigus Vulgaris consists of 2 phases. The first phase, Remission induction, includes management with systemic steroids and adjuvants like Rituximab, Azathioprine, and MMF. The second phase, Remission maintenance, involves maintaining patients with daily prednisolone of 10 mg or less along with the above-mentioned adjuvants. According to Dr. Neil, Rituximab acts like putting water on the fire in pemphigus.

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