Original Article

Low-dose rituximab as an adjuvant therapy in pemphigus

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Abstract

Background: Pemphigus is a chronic autoimmune blistering disease where systemic steroids and immunosuppressants are the mainstay of therapy, but long-term treatment with these agents is associated with many side effects. Rituximab, a chimeric monoclonal anti-CD20 antibody, in low doses has shown efficacy as an adjuvant to reduce the dose of steroids.

Aim: To study the clinical efficacy and safety of low-dose rituximab as an adjuvant therapy in pemphigus.

Methods: Fifty patients with extensive pemphigus were selected, who either had recalcitrant pemphigus, were steroid dependent, had relapsed after pulse therapy, had anti-desmoglein levels >20, had contraindications to conventional treatment or wanted to avoid conventional treatment and its side effects. Two doses of rituximab (500 mg) were given 2 weeks apart and patients were regularly followed up every 2 weeks for 3 months and then monthly upto 2 years. Complete blood counts, liver function tests, renal function tests, skin biopsy, direct immunofluorescence and desmoglein levels were checked before and after rituximab administration. Pre-rituximab chest X-ray and electrocardiograph were also obtained.

Results: At 3 months, 41 (82%) patients showed complete remission. Nine (18%) patients had partial remission. After 6–12 months, 20 (40% of enrolled patients) continued to be in remission and were off all systemic therapy and the remaining 19 (38%) were continuing to take low doses of steroids with or without other adjuvant immunosuppressants and 2 (4%) had to be given another 2 doses of rituximab and subsequently could be managed with low-dose steroids. Of the 9 patients in partial remission at 3 months, after 6–12 months 5 (10% of the total) were completely off treatment and went into complete remission and 4 (8%) were on additional treatment out of which 2 (4%) had to be given 2 additional doses of rituximab and were in partial remission with low-dose therapy at the end of 12 months. One patient developed urticaria as a side effect. Another developed herpes zoster.

Conclusion: Our results show that low-dose rituximab is a well-tolerated and beneficial adjuvant therapy in recalcitrant pemphigus which helps reduce both the severity of disease as well as the dose of steroids and immunosuppressants.

Key words: Adjuvant therapy, pemphigus, rituximab

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Introduction

Pemphigus is a chronic autoimmune bullous dermatosis, histologically characterized by intra-epidermal blister formation and immunopathologically by the presence of bound and circulating autoantibodies directed against the intercellular adhesion proteins of cutaneous and/or mucosal epithelial cells.[1] The incidence varies from 0.09% to 1.8% in dermatology outpatients.[2,3] It is mediated by pathogenic autoantibodies directed against desmoglein 1 and/or desmoglein 3.[4-6] Pemphigus vulgaris is the most common subtype,

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/ijdvl.IJDVL_1078_14

How to cite this article: Gupta J, Raval RC, Shah AN, Solanki RB, Patel DD, Shah KB, *et al.* Low-dose rituximab as an adjuvant therapy in pemphigus. Indian J Dermatol Venereol Leprol 2017;83:317-25.

Received: January, 2015. **Accepted:** December, 2015.

accounting for 75 to 92% of all pemphigus cases.[3,7] Dexamethasone-cyclophosphamide pulse therapy or long-term oral corticosteroids with or without adjuvant immunosuppressants such as azathioprine, cyclophosphamide and mycophenolate mofetil have been used for severe cases of pemphigus in India.[1,8] Though many treatment options are available, it still remains an unpredictable disease. The chronic immunosuppression resulting from treatment also increases the risk of infections and malignancy which ultimately lead to increased morbidity and mortality.[9] The challenge in pemphigus treatment, therefore, is to balance the risks of disease with risks of therapy. Thus, there is a constant search for newer and safer therapeutic modalities.

Rituximab is a chimeric human-mouse monoclonal anti-CD20 antibody. It is directed against CD20, a pan B-cell glycoprotein expressed on B lymphocytes from the pre-B cell through the preplasma-cell stage. Rituximab destroys B cells mainly through antibody-dependent cell-mediated cytotoxicity; other mechanisms include complement-mediated lysis, direct disruption of signaling pathways and triggering of apoptosis.[10] Rituximab is Food and Drug Administration (FDA) approved for use in non-Hodgkin's lymphoma (375 mg/m^2 once a week; total duration varies with type of lymphoma) and for rheumatoid arthritis (2 doses of 1000 mg given 2 weeks apart and repeated after few months if required).[11,12] It has several off-label uses too, such as systemic lupus erythematosus, myasthenia gravis and for autoimmune blistering disorders. The first blistering disease to respond to rituximab was paraneoplastic pemphigus with B-cell non-Hodgkin lymphoma.[13-15] The most common regimen used is the lymphoma protocol.[16-19] As pemphigus is not a malignant disease, a lower dose of rituximab (500 mg at 2 weeks interval) can suffice and such dosing is reported to have a better side effect profile.[20]

Our main aim was to assess the benefit of low-dose rituximab as an adjuvant therapy for pemphigus, particularly in cases difficult to treat conventionally, to study its clinical efficacy and safety.

Methods

Patients

Informed consent and permission from the ethics committee was taken. Fifty pemphigus patients, who were difficult to treat using conventional therapy, were enrolled and received injection rituximab 500 mg at 2 weeks intervals as an adjuvant to their existing treatment modalities between October 2012 and March 2014. Inclusion criteria included at least one of the following:

a. Patients with recalcitrant pemphigus who had either failed to respond (i.e., developed fresh crops of new lesions or had extension of old lesions), or responded but with frequent recurrences, while on long-term high dose oral prednisolone (40–60 mg/day for 12 weeks), with or without additional immunosuppressive therapy
b. Patients with recurrent relapse after dexamethasone-cyclophosphamide/dexamethasone-azathioprine pulse therapy, (i.e., fresh crop of lesions or extension of old lesions) after completing 9 cycles of dexamethasone-cyclophosphamide or dexamethasone-azathioprine pulse therapy
c. Patients with desmoglein antibody (anti-desmoglein-1 and/or anti-desmoglein-3) levels >20
d. Steroid dependence, i.e., patients being treated with prednisone 30–40 mg/day for more than 1 year and in whom lowering of dose resulted in a fresh crop of lesions
e. Contraindications to the use of conventional therapy
f. Unwillingness to continue conventional therapies.

Exclusion criteria included patients with pregnancy, breastfeeding, active hepatitis, human immunodeficiency virus infection, widespread infections and cardiac disease.

Diagnoses were confirmed by classical clinical presentation, histology, direct immunofluorescence and ELISA assays of antibodies to desmoglein 1 or 3.

All patients had been treated in the past for periods varying between 5 months and 10 years with some or all conventional regimens such as prednisolone 1–1.5 mg/kg/day, cyclophosphamide 1–2 mg/kg/day, azathioprine 1–2 mg/kg/day and dexamethasone-cyclophosphamide pulses or dexamethasone-azathioprine pulses.

Pretreatment workup

Skin biopsies from all patients were submitted for histological assessment using hematoxylin-eosin staining. A perilesional biopsy was also sent for direct immunofluorescence. Serum anti-desmoglein antibody levels were determined before infusion and repeated 1 month after infusion and subsequently every 3 months for upto 2 years. Pretreatment workup included a complete hemogram, liver function tests, renal function tests, fasting and postprandial blood sugar levels, chest X-ray, electrocardiogram, Mantoux test, screening for viral infections including Hepatitis B, Hepatitis C, human immunodeficiency virus-1 and human immunodeficiency virus-2, and serum IgG.

Treatment protocol

Patients were premedicated with hydrocortisone (100 mg), pheniramine maleate (8 mg), and paracetamol (1 g) intravenously 30 minutes prior to infusion. On the day of infusion, antibiotic coverage was given with two doses of injection ceftriaxone 1 g intravenously 12 hours apart.

Injection rituximab (500 mg) in 500 ml of normal saline solution was given over 6 hours and a second dose was given after 2 weeks. Vitals were monitored every 15 minutes and patients were watched for hypotension, nausea, headache, chills, fever and rashes. Two additional doses were given 6 months after the first treatment in case of failure (non-healing old lesions, appearance of new lesions which did not heal within 2 weeks and consistently positive anti-desmoglein-1 and anti-desmoglein-3 levels).

Monitoring and follow up

To determine the response, we calculated the pemphigus activity severity score published by Herbst and Bystryn and used by Londhe *et al*.[21,22] It was calculated pre-infusion and at 3 months, post 2nd infusion.

Patients were followed up every 2 weeks for 3 months after the second infusion followed by monthly follow-up for up to 2 years. Endpoints were defined as complete remission off therapy (no lesions and no therapy), complete remission on treatment with low-dose steroids or some immunosuppressant, partial remission (1-2 lesions/<2% body area involvement) off therapy and on therapy. Follow-up duration of our patients after the second dose of rituximab ranged from 12–25 months with a median of 17 months.

Results

Patient characteristics

Fifty patients were included in this prospective study; 9 had pemphigus foliaceus and 41 had pemphigus vulgaris. Our study

subjects included 30 females and 20 males aged between 9 to 65 years (median 38 years, mean 35.7 years). The use of rituximab in the pediatric age group is restricted, mainly because of limited experience. However, some studies have been published in this regard.[23-29] Our series of patients included 5 pediatric patients (who were not responding to any other kind of therapy). The duration of pemphigus in our patients ranged from 6 months to 10 years (median 2 years, mean 1.5 years). Of all patients, 26 had steroid dependence (were being treated with prednisone 30–40 mg/day for more than 1 year and dose reduction resulted in fresh lesions); 12 patients were refractory to conventional treatment (6 had recalcitrant pemphigus and 6 had relapsed after receiving 9 cycles of dexamethasone-cyclophosphamide pulse/dexamethasone-azathioprine pulse therapy); 5 had developed morbidity due to medication and hence had contraindications to the continued use of conventional therapy; and, 7 were unwilling to continue with conventional therapies due to their side effects and wanted to try new medication. Other comorbidities are mentioned in Table 1.

The interval between two infusions was 2 weeks in 47 patients and 3 weeks in 3 patients (one developed herpes zoster and the other two came late for follow-up).

Clinical efficacy and relapse rate of rituximab on pemphigus

Forty-one (82%) of 50 patients had a complete remission either on or off treatment and 9 (18%) patients showed only partial remission at the end of 3 months [Figures 1-6].

After 6 months, 20 of 50 enrolled patients (40%) maintained complete remission and were off all systemic therapy, 19 (38%) patients were continuing with low dose steroids (prednisolone 5–20 mg/day) with or without immunosuppressants and 2 (4%) had a relapse and had to be given additional 2 doses of rituximab. Of 9 patients in partial remission after 6 months, 5 (10%) were completely off treatment and went into complete remission and 4 (8%) were on additional treatment out of which 2 (4%) had a relapse and had to be given 2 additional doses of rituximab [Figure 7]. Thus, overall, 8% had relapsed (patients with persistent new lesions not healing with low dose steroids/immunosuppressants and topical treatment in 2 weeks) but were successfully treated with 2 extra doses of rituximab. They all achieved remission within 52 weeks post-treatment [Figure 7].

At the end of 12 months, 25 out of 50 patients were still on therapy with immunosuppressants and/or steroids. Of these, 12 were on only low-dose steroids (prednisolone 5–20 mg/day) [Figure 8].

Twenty-four patients had 24 months follow-up. At the end of 24 months, 20 (83.3%) were in complete remission with only one of them on treatment and 4 (16%) were in partial remission on treatment (two with low-dose steroid alone and two with low-dose steroid and azathioprine) [Figure 7].

Serological evaluation of antidesmoglein-1 and antidesmoglein-3 and pemphigus activity score severity score evaluation

The mean pre-treatment anti-desmoglein-1 level was 132.9 and post-treatment, 1 month after the second dose of rituximab, it fell to 51.6. The mean pre-treatment anti-desmoglein-3 level was 138.3, which dropped to 39.48, a month after the second dose [Table 2].

The mean pre-treatment pemphigus activity score was 7.98 (range 3–9), which reduced to 1.24 (0–6) 3 months after the second dose

Table 1: Patient information and follow-up

Age/sex	Diagnosis	Previous DCP/DAP	Previous steroids/ immunosuppresants	Comorbidity	Postrituximab RX (immunosuppressants at 12 months)	Postritux RX (steroids-12 months)	Follow-up at 3 months	Follow-up at 6 months	Follow-up at 12 months
21/male	Pemphigus vulgaris	DCP	ST 30 OD + AZ 50	-	AZ 50	ST 10 OD	CR	CR	CR
36/female	Pemphigus vulgaris		ST 40 OD + CY 50	Diabetic		ST 15 OD	PR	PR	PR
46/female	Pemphigus foliaceus		ST 30 OD	Anemic	-	ST 5 OD	CR	CR	CR
65/male	Pemphigus vulgaris		ST 20 OD	HT	-	Off RX	CR	CR	CR
35/male	Pemphigus vulgaris		ST 40 OD + CY 50	Diabetic	CY 50	ST 10 OD	CR	CR	CR
36/female	Pemphigus vulgaris		ST 40 OD + AZ 50		AZ 50	ST 15 OD	PR	PR	PR
33/male	Pemphigus vulgaris	DCP	ST 20 OD			ST 5 OD	CR	CR	CR
24/female	Pemphigus vulgaris	DAP	ST 15 OD			Off RX	CR	CR	CR
36/female	Pemphigus vulgaris		ST 40 OD + AZ 50		-	Off RX	CR	CR	CR
36/female	Pemphigus vulgaris		ST 40 OD + AZ 50	Diabetic	-	ST 5 A/D	CR	CR	CR
48/male	Pemphigus foliaceus		ST 40 OD + CY 50		CY 50	ST 5 BD	CR	CR	CR
48/male	Pemphigus vulgaris		ST 40 OD			ST 5 OD	PR	PR	PR
54/male	Pemphigus vulgaris		ST 40 OD + AZ 50			Off RX	CR	CR	CR

Contd...

Table 1: Continued...

Age/sex	Diagnosis	Previous DCP/DAP	Previous steroids/ immunosuppresants	Comorbidity	Postrituximab RX (immunosuppressants at 12 months)	Postritux RX (steroids-12 months)	Follow-up at 3 months	Follow-up at 6 months	Follow-up at 12 months
45/female	Pemphigus vulgaris		ST 40 OD + AZ 50			Off RX	CR	CR	CR
47/female	Pemphigus foliaceus		ST 30 OD + AZ 50			Off RX	CR	CR	CR
30/female	Pemphigus vulgaris		ST 20 OD + AZ 50	Anemic	-	Off RX	CR	CR	CR
28/female	Pemphigus vulgaris	DCP	ST 40 OD + CY 50		CY 50	ST 5 A/D	CR	CR	CR
21/male	Pemphigus foliaceus		ST 20 OD + AZ 50		-	Off RX	CR	CR	CR
37/female	Pemphigus foliaceus		ST 20 OD + AZ 50		-	Off RX	CR	CR	CR
46/female	Pemphigus vulgaris		ST 40 OD + AZ 50	HT		Off RX	PR	PR	CR
65/female	Pemphigus vulgaris		ST 40 OD + AZ 50	Diabetic, HT, cataract		ST 15 OD	CR	CR	CR
35/male	Pemphigus foliaceus		ST 40 OD + AZ 50			ST 5 BD	CR	CR	CR
36/female	Pemphigus vulgaris		ST 40 OD + AZ 50		AZ 50	ST 10 OD	CR	CR	CR
33/male	Pemphigus vulgaris	DCP	ST 40 OD + CY 50		-	Off RX	PR	PR	CR
21/male	Pemphigus vulgaris		ST 40 OD + AZ 50		-	ST 5 A/D	CR	CR	CR
38/female	Pemphigus vulgaris		ST 40 OD + AZ 50		-	Off RX	CR	CR	CR
46/female	Pemphigus vulgaris		ST 30 OD + CY 50		CY 50	Off RX	CR	CR	CR
65/female	Pemphigus vulgaris		ST 40 OD + AZ 50	Diabetic, HT, cataract		Off RX	CR	CR	CR
35/male	Pemphigus foliaceus	DCP	ST 40 OD + CY 50		-	ST 5 OD	CR	CR	CR
36/female	Pemphigus vulgaris		ST 40 OD		-	Off RX	CR	CR	CR
33/male	Pemphigus vulgaris		ST 40 OD + CY 50		CY 50	Off RX	CR	CR	CR
21/male	Pemphigus vulgaris		ST 40 OD + AZ 50			Off RX	CR	CR	CR
38/female	Pemphigus vulgaris		ST 30 OD + AZ 50	HT		Off RX	CR	CR	CR
46/female	Pemphigus foliaceus		ST 40 OD + CY 50		CY 50	Off RX	CR	CR	CR
65/female	Pemphigus vulgaris		ST 40 OD + AZ 50	Diabetic, HT	-	ST 5 A/D	CR	CR	CR
35/male	Pemphigus vulgaris		ST 40 OD		-	Off RX	PR	PR	CR
36/female	Pemphigus vulgaris		ST 40 OD		-	Off RX	PR	PR	CR
33/male	Pemphigus foliaceus		ST 40 OD + AZ 50		-	ST 5 OD	CR	CR	CR
21/female	Pemphigus vulgaris		ST 30 OD		-	Off RX	CR	CR	CR
32/male	Pemphigus vulgaris		ST 40 OD + AZ 50			Off RX	CR	CR	CR
49/female	Pemphigus vulgaris		ST 40 OD + CY 50	Anemic	CY 50	Off RX	CR	CR	CR
21/female	Pemphigus vulgaris		ST 40 OD		-	Off RX	PR	PR	CR
42/male	Pemphigus vulgaris		ST 40 OD + AZ 50			ST 5 OD	CR	CR	CR
19/female	Pemphigus vulgaris		ST 40 OD + CY 50	Anemic	CY 50	ST 5 OD	CR	CR	CR
51/female	Pemphigus vulgaris		ST 20 OD	Anemic		Off RX	CR	CR	CR
12/male	Pemphigus vulgaris		ST 40 OD + AZ 50		-	Off RX	CR	CR	CR
9/female	Pemphigus vulgaris		ST 40 OD + AZ 50	Anemic	-	Off RX	CR	CR	CR
11/female	Pemphigus vulgaris		ST 40 OD + CY 50		CY 50	Off RX	CR	CR	CR
12/male	Pemphigus vulgaris		ST 40 OD + CY 50		CY 50	ST 5 OD	PR	PR	PR
9/male	Pemphigus vulgaris		ST 40 OD + AZ 50			Off RX	CR	CR	CR

CR: Complete remission, PR: Partial remission, DCP: Dexamethasone-cyclophosphamide pulse, DAP: Dexamethasone-azathioprine pulse, ST: Steroid, CY: Cyclophosphamide, AZ: Azathioprine

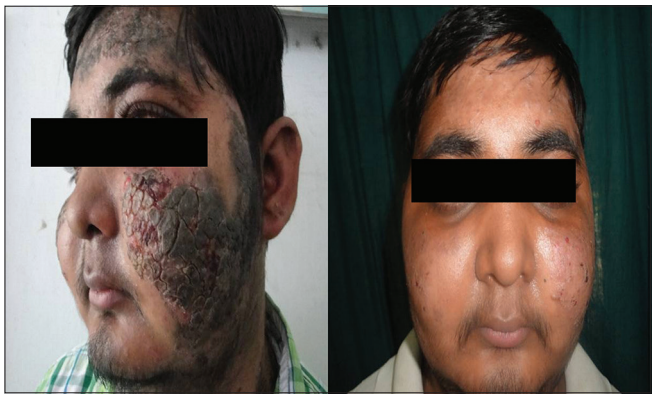

Figure 1: Image of a patient before receiving rituximab and 3 months after 2nd infusion

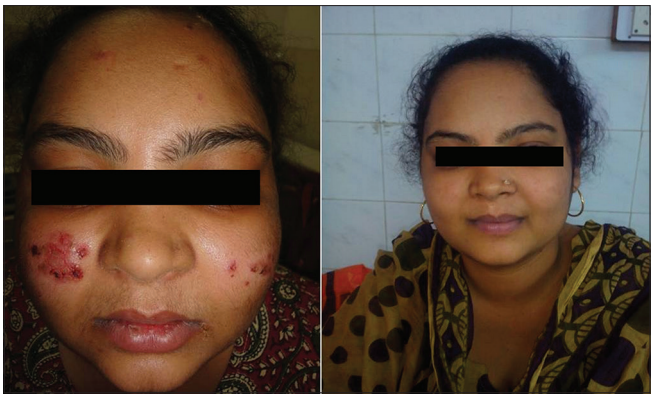

Figure 2: Image of a patient before receiving rituximab and 3 months after 2nd infusion

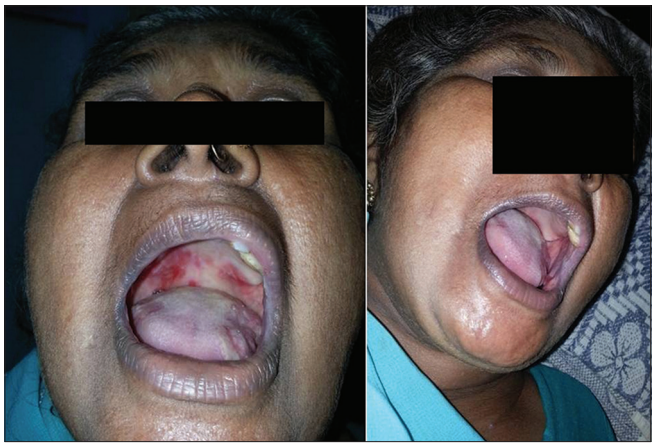

Figure 3: Image of a patient before receiving rituximab and 3 months after 2nd infusion

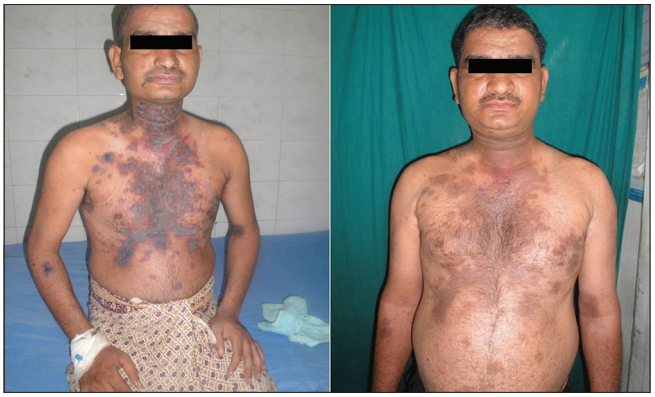

Figure 4: Image of a patient before receiving rituximab and 3 months after 2nd infusion

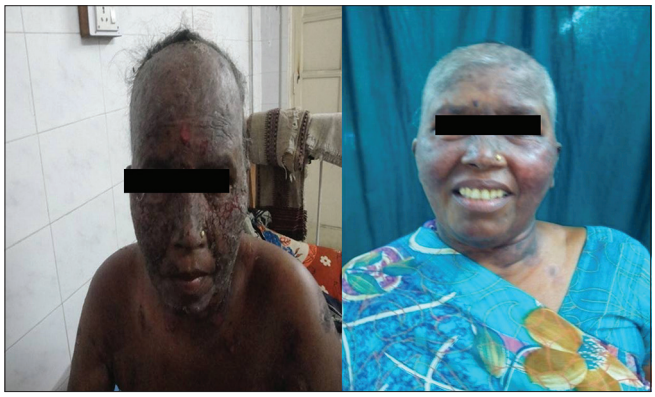

Figure 5: Image of a patient before receiving rituximab and 3 months after 2nd infusion

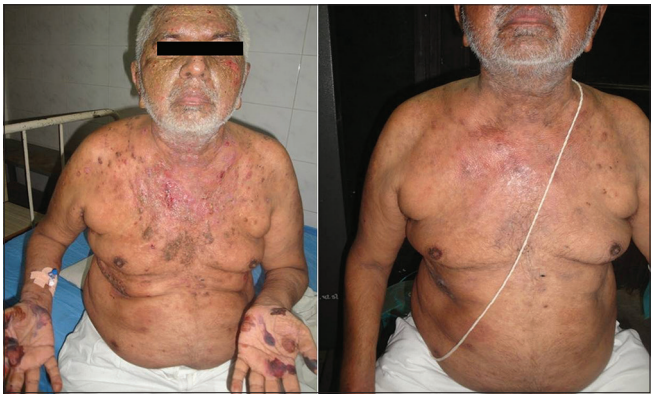

Figure 6: Image of a patient before receiving rituximab and 3 months after 2nd infusion

[Table 3]. The maximum possible value of the severity score used was 10; extent of disease received 0 to 4 points and intensity of therapy received 0 to 6 points.[21]

Adverse effects

One patient developed chills, one had urticaria following infusion, one had decreased blood pressure and one developed herpes zoster which was managed without any complication. No major side effects were encountered.

Discussion

The optimal dosage of rituximab for pemphigus has not been clearly defined. A recent study using modified lymphoma protocol by Londhe *et al.* showed 79% complete remission in 9/19 in whom all other treatment could be stopped and 10 remained on minimal dose of steroids and immunosuppresants at 9 months.[22] In a review by Zakka *et al.*, 180 patients were treated with the lymphoma protocol and 92 patients were treated with the rheumatoid arthritis protocol and complete remission occurred in 66.7% patients on lymphoma

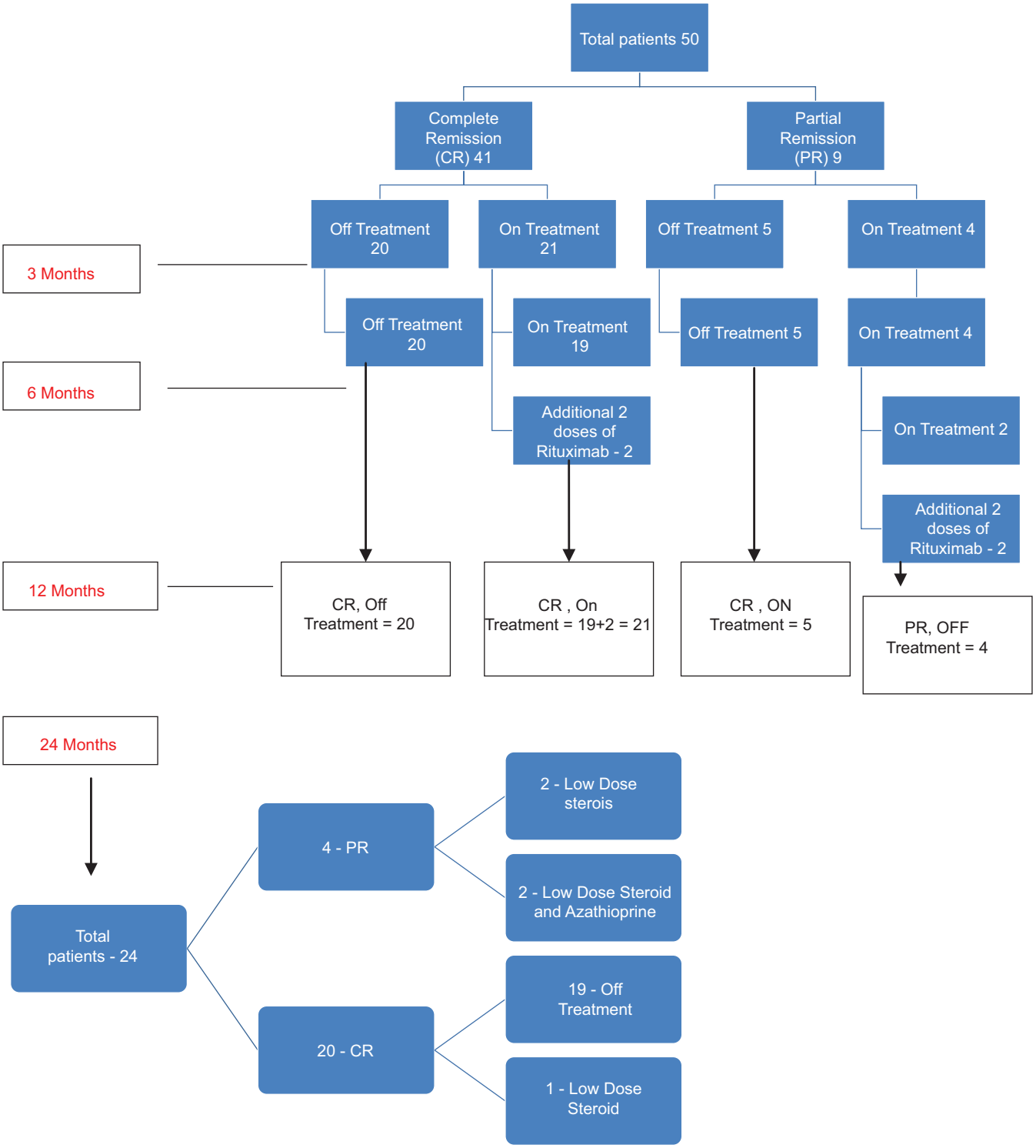

Figure 7: Flow chart representing the response to rituximab. CR: Complete remission, PR: Partial remission, On Rx: On low dose steroids and/or other immunosuppressants, Off Rx = Not on oral steroids or other immunosuppressants

protocol and 75% in rheumatoid protocol.[30] Several cases have been published using both lymphoma protocol and rheumatoid protocol. Currently, there is no consensus for the dosing of rituximab in pemphigus; a study by Kanwar *et al.*, comparing 2 doses of 1000 mg given 2 weeks apart and 2 doses of 500 mg given 2 weeks apart with 11 patients in each group, showed that there was a difference in anti-desmoglein levels and a higher relapse rate with lower dosing, but no statistically significant difference in clinical outcomes or relapse rates between the two regimens.[31]

Our prospective open study demonstrates success with low-dose rituximab in a series of 50 patients. The dose of 500 mg, 2 weeks apart, has been used before.[20,31] It is 39% and 50% of the doses used in hematology and rheumatology, respectively, thus cutting the

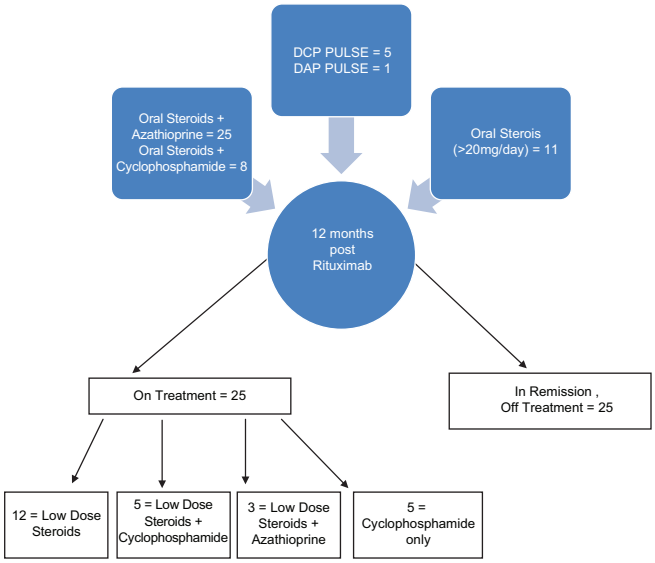

Figure 8: Patients on additional treatment besides rituximab at 12 months. High dose steroids ≥30 mg/day, Low dose steroids ≤20 mg/day

cost of the treatment to half or less. Horváth *et al.* demonstrated complete remission in 52% patients (median follow-up 22 months) with the same protocol as used in our study.[20] In comparison, we saw complete remission (either on or off other treatment) in 82% of our patients within 3 months of adjuvant rituximab therapy. At the end of 1 year, 25 (50%) of our patients were in complete remission off all treatment, while the remaining 25 continued to be on additional low dose steroids and/or immunosuppresants [Figure 8], with no more relapses till date minimum 12 months follow-up. Thus, we achieved a success rate higher than that reported in the existing studies with any of the established protocols for other conditions. The variation in results and findings could be due to different genetic makeup of our patients which contributed to their requirement of lower doses.

There are no double-blinded, randomized trials available comparing the conventional dexmethasone-cyclophosphamide pulse therapy with rituximab. Indian patients usually show a good response to conventional dexamethasone-cyclophosphamide pulse and oral corticosteroids. However, some patients are resistant to conventional therapy or have contraindications for their use or become steroid-dependent. After a mean duration of 12 months of follow-up, all our patients had responded, 25 of these patients were not receiving any systemic therapy. The four patients who relapsed showed a correlation of anti-desmoglein-1 and anti-desmoglein-3 titers with disease activity. Among the patients who responded initially, 5 had earlier been treated with dexamethasone-cyclophosphamide pulse and 43 had been given high-dose (>30 mg/day) steroids. Overall, treatment with rituximab resulted both in major clinical improvement and a large decrease in the doses of corticosteroids and immunosuppressants; 25 patients who were earlier on daily steroids could be weaned off them. For 20 patients who continued to need daily steroids, the mean daily requirement fell from 35 mg to 15 mg and in 26 out of 39 patients needing other immunosuppressants at the start of the study, they could be stopped.

In the majority cases of pemphigus vulgaris (37 out of 41), disease severity correlated with anti-desmoglein-3 levels. There was a 72.1% fall in the mean anti-desmoglein-3 level at the end of 1 month

Table 2: Anti-desmoglein antibody levels: Desmoglein 1-negative 0-14, intermediate 14-20, positive >20, Desmoglein 3-negative 0-7, intermediate 7-20, positive >20

Age/sex	Pre-Dsg1	Post-Dsg1	Pre-Dsg3	Post-Dsg3
21/male	15	1.8	76	5.7
36/female	150	67.54	347	20.36
46/female	277	108	12	9
65/male	87.8	61	261	124.9
35/male	130	2.82	248	69.4
36/female	30	8.38	38	5.65
33/male	3.4	2.9	99.1	25.7
24/female	9.1	0.96	103.8	16.65
36/female	283	190	80.5	31.5
36/female	25	12	76.3	45.6
48/male	10	9.7	186.6	121.9
48/male	260	210	240	189
54/male	98	49	9	7
45/female	11.5	9.7	174.1	92.7
47/female	54	6.6	360.8	5.4
30/female	62	8.8	3.9	1.1
28/female	48.5	9.4	9.3	3.2
21/male	332.6	81.1	5.7	3.2
37/female	53.8	33.2	117.4	74.1
46/female	126	88.4	293	41.1
65/female	62.1	12.1	6.2	3.9
35/male	220.3	130.4	161.6	31.1
36/female	221	167	224.1	111.1
33/male	258	141.4	216.9	97.1
21/male	211.1	131.4	194	81.8
38/female	277	98	86	12
46/female	80	21.2	240	38.4
65/female	188	43.1	88	17
35/male	81.4	41.2	198.9	42.3
36/female	233.4	66.3	106.6	12
33/male	33.4	21.1	158	11.1
21/male	5.7	1.8	189.4	15
38/female	53.8	33.2	145	27.3
46/female	261	87.8	63.5	12.7
65/female	248	2.8	69.4	1.3
35/male	98.5	8.3	64.9	5.6
36/female	220.8	22.9	194.3	7.5
33/male	83.9	30.4	37	9
21/female	20.2	15.8	143.4	18.7
32/male	237	80.54	194.6	184.6
49/female	228	49	229	44
21/female	90.9	54.4	94.8	61
42/male	108	33.4	201	11.7
19/female	44	39.7	145	27.3
51/female	193	56	278	43
12/male	31.8	11.3	17.1	3.1
9/female	357	98	219	77
11/female	99.1	3.4	103.4	6.7
12/male	184.6	80.5	94	64
9/male	150	47	10.8	1.8

Pre-Dsg1 and Dsg3 were done 2-5 days before giving the first infusion of rituximab, Post-Dsg1 and Dsg3 were done at 1 month follow-up after second infusion. Dsg1: Desmoglein 1, Dsg3: Desmoglein 3

Table 3: Pemphigus activity score pre and post rituximab infusion

Age/sex	PAS	
	Pre	Post
21/male	8	1
40/female	7	2
46/female	8	1
65/male	9	1
35/male	7	0
36/female	7	0
33/male	9	2
24/female	7	1
36/female	8	2
40/female	8	1
48/male	7	2
48/male	9	2
54/male	8	1
45/female	8	2
47/female	10	1
30/female	9	0
28/female	7	2
21/male	7	1
40/female	7	1
46/female	8	1
65/female	9	2
35/male	9	1
36/female	7	0
33/male	8	1
21/male	8	1
40/female	7	0
46/female	8	1
65/female	9	1
35/male	9	1
36/female	8	0
33/male	8	1
21/male	7	1
40/female	7	0
46/female	8	1
65/female	7	2
35/male	8	2
36/female	7	1
33/male	8	1
21/female	7	2
32/male	9	2
49/female	8	2
21/female	8	2
42/male	7	2
19/female	8	1
51/female	8	2
12/male	9	2
9/female	9	1
11/female	8	2
12/male	9	2
9/female	9	1

Pre-PAS was calculated before the first infusion of rituximab, Post-PAS at 3 months of follow-up after the second infusion of rituximab. PAS: Pemphigus activity score

except some which remained positive immediately post-treatment [Table 2] and most of them required additional low-dose steroid and immunosuppressants. The mean pemphigus activity score fell from 7.98 to 1.04 at the end of 3 months which is similar to what was seen in the study by Londhe *et al*. (5.58 to 2.04).[29]

The use of rituximab is associated with adverse effects. However, as observed in our study, using low doses helped to reduce the side effects. The adverse effects can be immediate: infusion-related - such as allergic responses, immediate cardiac effects, pulmonary embolism; or late ones like severe infections (10%) such as fatal septicemias seen in the study by Joly *et al*.[32] In our study, only one patient developed mild infusion reaction during the first infusion, subsequent infusions being uneventful. These reactions tend to resolve upon slowing infusion rates or addition of corticosteroids, antipyretics and antihistamines and do not recur in subsequent infusions.[33] Only one patient (2%) developed herpes zoster. None of our patients exhibited late serious side effects. There were no fatalities in our study. No patient experienced a serious adverse event, namely pulmonary embolism or deep venous thrombosis. Other late adverse effects have been described including late-onset neutropenia reported 3–23 weeks after rituximab infusion.[34,35] None of our patients developed this side effect.

Conclusion

Low-dose rituximab can induce a prolonged clinical remission in pemphigus with minimal side effects. It is a fairly well-tolerated adjuvant therapy which helps to reduce both the severity of disease as well as the dose of steroids and immunosuppressants. As the optimal dose of rituximab is not known, further randomized trials are needed to determine the dose and they need to take cost-effectiveness ratios into account. This is especially applicable to a resource-poor setting like India. Factors limiting the use of rituximab include its high cost and limited knowledge of long-term adverse effects. Once these hurdles are overcome, it can be considered an adjuvant for the treatment of pemphigus, thus reducing the use of other immunosuppressants and thereby reducing the burden of their long-term use including adverse effects, continuous hospitalizations and lowered quality of life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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