

Sustained Remission of Pemphigus in Indian Patients with A Modified Lymphoma Rituximab Protocol

Sharad Dattatraya Mutalik, Yashashree Dhaval Rasal

Sharad Dattatraya Mutalik, Yashashree Dhaval Rasal, Department of Dermatotherapy and Cosmetology, Joshi Hospital, Maharashtra Medical Foundation, 778 Deccan Gymkhana, Shivaji Nagar, Pune, Pin Code 411004, India.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Sharad D. Mutalik, Planet Skin, 1st Floor, Samruddhi Apartments, 95/A/2, Shivaji Nagar, Near Pmc Bus Terminus, Near Shramik Bhavan, Pune, Maharashtra State, India.

Email: sharadmutalik.skindoctor@gmail.com

Telephone: +91-20-41096702/703

Received: December 9, 2017

Revised: February 25, 2018

Accepted: February 28, 2018

Published online: June 6, 2018

ABSTRACT

AIM: Rituximab is a proven gratifying therapeutic modality for pemphigus of varying severity. While defined guidelines for its use in pemphigus are awaited, we treated patients with a modified lymphoma protocol of rituximab in an attempt to add on to the search for an ideal dosing schedule.

MATERIALS AND METHODS: We studied retrospectively a total of 10 patients with pemphigus in a private practice setup offering facility of hospitalized care with rituximab as 10 infusions over a period of 7 months with a mean follow up period of 6 years. Patients had varying severity of disease and had not received rituximab in the past.

RESULTS: Complete remission was observed in 100% patients. The mean time to disease control and time for complete remission was 4.2 weeks and 14 weeks respectively. 4(40%) patients were in complete remission and were off all treatment. 4(40%) patients were in complete remission with adjuvant immunosuppressant. 2(20%) patients experienced relapse after a mean duration of 2.5 years and were treated with rituximab again without corticosteroids which induced new complete remission. No serious adverse effects were observed.

CONCLUSIONS: Long term treatment with rituximab for pemphigus of varying severity over 7 months was safe, well tolerated enabling steroid discontinuation and achieving uniform sustained remission up to 6 years in all treated patients.

Key words: Pemphigus; Rituximab; Long-term remission; Modified lymphoma protocol

© 2018 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Mutalik SD, Rasal YD. Sustained Remission of Pemphigus in Indian Patients with A Modified Lymphoma Rituximab Protocol. *Journal of Dermatological Research* 2018; **3(1)**: 135-138 Available from: URL: <http://www.ghrnet.org/index.php/jdr/article/view/2206>

Abbreviations

AZP: Azathioprine; CR: Complete remission; CYC: Cyclophosphamide; DCP: Dexamethosone Cyclophosphamide pulse; F: Female; IV IG: Intravenous Immunoglobulins; M: Male; MMF: Mycophenolate mofetil; MPD: Methyl prednisolone; OFF: Off therapy; ON: On therapy; PE: Pemphigus erythematosus; PD: Prednisolone; PV: Pemphigus vulgaris; R: Relapse; Sr No: Serial number; TCR: Time for complete remission; TDC: Time to disease control; W:Weeks; Y:Year

INTRODUCTION

The emergence and subsequent success of rituximab in treatment for pemphigus has been a deliverance for patients; battling both the onslaught of a relentlessly progressive disease and the burden of its long term treatment in the form of global immunosuppressants^[1].

The standard rituximab protocols currently in use for the treatment of pemphigus viz. the lymphoma protocol and the rheumatoid arthritis protocol give predictable remission, however relapses requiring retreatment is common^[2]. Various modifications are being attempted to achieve an dosing schedule which gives sustained remission.

Despite its high cost compared to traditional choices of corticosteroids and/or immunosuppressant, rituximab is rapidly gaining favor as the preferred treatment modality for pemphigus in India.

In India, pemphigus is relatively common and tends to occur at an earlier age; usually around the 3rd-4th decade. Higher incidence of pemphigus vulgaris and earlier age of onset seen in India has been attributed to higher frequency of DSG3*TCCCC in Indian population where patients had significantly increased frequency of HLA-DQB1*0302. Thus genetic susceptibility may be an important determinant in epidemiological difference of pemphigus in India. Therefore remissions achieved by rituximab therapy have offered dramatic improvement in the quality of life in these young pemphigus patients. Prima facie it is an expensive option to the patient but in the long run it has proven to be cost effective with fewer hospital admissions, allowing rapid tapering of global immunosuppressant with no long term adverse effects^[3,4].

We present herewith our experience of treating pemphigus with a modified long term lymphoma regimen in 10 patients, comprising a total of 10 infusions of rituximab spread over 7 months. The results analyzed retrospectively showed all patients achieving gratifying clinical recovery with sustained long term complete remission. 80% of treated patients have been observed to be lesion free since last 72 months. 20% relapsed after a mean of 2.5 years only to achieve remission till date with additional doses of rituximab.

METHODS

We performed a single centre retrospective review analysis of 10 patients with pemphigus treated with a modified lymphoma dosing of rituximab infusions at a private setup in western part of India. Since this was a retrospective study ethical committee approval was not sought for. Patient demographics are detailed in table 1. All patients were diagnosed clinically and diagnosis was confirmed by histopathological examination of skin biopsies using Haematoxylin –eosin staining. Direct Immunofluorescence and serum Anti Desmoglein autoantibody levels were not carried out due to the cost limitations. Data was collected retrospectively from the medical records of patients with pemphigus who had received rituximab. Initial indications were longstanding disease burden with severe, relapsing or recalcitrant disease. All rituximab naïve patients received 10 infusions of over a period of 7 months (Table 1).

The disease duration of 10 patients ranged from 2 years to 12 years with a mean of 4.8 years. Most patients were receiving oral corticosteroids in dosages varying from 60 mg/day to 20 mg/day in spite of which disease control had not been achieved. The median duration from diagnosis to 1st rituximab infusion was 42 months (range 24-144).

375 mg/m² of body surface area (BSA) of rituximab was infused once a week for 4 consecutive weeks followed by 375 mg/m² BSA once a month for 6 consecutive months. The response to therapy was determined according to the definition of an International Consensus Conference^[5]. Complete remission off therapy (CR) is the absence of new or established lesions while the patient is not receiving any systemic therapy for at least 2 months. Complete remission on therapy is the absence of new or established lesions while the patient

is receiving minimal therapy. Partial remission off therapy is the presence of transient new lesions that heal within one week without treatment while the patient is not receiving any systemic therapy for at least 2 months. Partial remission on minimal therapy is the presence of transient new lesions that heal within one week while the patient is receiving minimal; therapy including topical steroids. Relapse is the appearance of 3 or more new lesions each month that do not heal spontaneously within one week or the extension of established lesions in a patient who has achieved disease control. All patients had received systemic therapies (corticosteroids or immunosuppressive medications) before rituximab therapy. Most patients continued to receive concomitant adjuvant corticosteroid or immunosuppressive treatment for the 1st month of weekly cycles. Depending on the adequacy of response adjuvant treatment were/were not discontinued. The response to therapy and remission were assessed by clinical evaluation only. During the rituximab infusion possible adverse effects such as infusion reaction, hypersensitivity, nausea, fever, tachycardia were monitored. After completion of infusions follow up was conducted every 3 monthly for 2 years, then 6 monthly for the next 4 years for clinical evaluation of disease activity if any and lab investigations. At each visit long term adverse effects including leukopenia neutropenia and opportunistic infections were sought out for.

RESULT

The mean time to disease control (TDC) was 4.2 weeks after 1st infusion of rituximab when new lesions ceased to form and established lesions began to heal. All patients could be weaned off the steroids at this juncture.

The time to complete remission (TCR) was 14 weeks wherein the patient had been lesion free for 2 months at least.

All patients experienced complete remission. Of these 40 % maintained remission without any adjuvant therapy over 60 months while another 40% remained lesion free with adjuvant immunosuppressive viz. azathioprine (1-2 mg/kg/day).

20% showed relapse after a mean of 2.5 years. These included a patient with severe longstanding pemphigus vulgaris and a patient with pemphigus erythematosus. Relapses were mild in both the cases and resolved within 1 month without the need for additional medications apart from 2 doses of rituximab as 375 mg/m² BSA infusions given 2 weeks apart. Both patients have remained lesion free till date.

Neither immediate nor delayed complications arose in any of the studied patients (Table 2).

Table 1 Patient Demographics.

Characteristics	Patients (n = 10)
Male/Female	4/6
PV/PF/PE	8/1/1
Presence of mucosal lesions	9(90%)
Median age at diagnosis (years)	37.5
Previously treated with corticosteroids	10(100%)
Previously treated with corticosteroid sparing drugs	6(60%)
Cyclophosphamide	3
Azathioprine	3
Mycophenolatemofetil	1
Intravenous Immunoglobulins	1
Median age at the time of first dosing of Rituximab (years)	42
Median duration of follow up(years)	4

DISCUSSION

The optimal dosing regimen of rituximab for autoimmune vesiculobullous disorders yet eludes the dermatologist. Some patients achieve a fundamental change in B-cell status and do not experience subsequent relapses after the first treatment cycle others require repeated treatment.

Our results show that the modified oncologic protocol is effective in achieving complete remission in all patients of pemphigus with or without adjuvant immunosuppressant. 80% patients never experienced relapse. Of these 50% are in complete remission without any concomitant therapy while 50% have maintained complete remission with supplemental immunosuppressive azathioprine given concomitantly in dose of 50-100 mg/day (ie.1-2 mg/kg/day). Rituximab was well tolerated with no observed adverse effects in any of the treated patients. 20% patients with relapse responded to repeat rituximab therapy with remission. See Figures 1-6 showing response to rituximab therapy in two patients.

A retrospective study carried out by Sharma et al in central northern and eastern India, 21 patients received rituximab by the rheumatology regimen and 4 patients by modified regimens. Complete remission was obtained in 88% of patients and partial remission in 12%. Relapse rates were recorded to be at 16%. TDC was 1.10 months whereas TCR was 4.36 months. Oral prednisolone was administered at a dosage of 0.5 mg/kg of body weight and tapered over 3-4 months according to disease activity. The mean total dose of oral prednisolone after rituximab infusion was 3535.64 mg. Relapses occurred after a mean duration of 9.5 months (range 2-24 months) in 10 patients who had received high dose of oral steroids and other immunosuppressive for a period greater than 1 year. Relapses were noted in recalcitrant cases and within 1 month of discontinuation of oral prednisolone. Relapses were mild and resolved in 1 month without the need of additional medication. 10.5% of patients developed serious infections. Paradoxical exacerbation of disease activity was seen with 2 patients. Majority of patients received concomitant immunosuppressant's during treatment with Rituximab^[6].

However, there is a paucity of case studies using lymphoma protocol of rituximab for the treatment of pemphigus in the Indian scenario. In a study by Londhe et al, 24 patients treated by one injection of rituximab per week for 3 consecutive weeks by 375 mg/m² BSA with the 4th infusion 3 months after 3rd dose, resulted in CR in 12 patients without systemic therapy^[7]. Complete remission with low dose steroid and Immunosuppressant was achieved in 7 patients. 5

patients had partial remission. Relapse in 2 patients needed moderate dose of oral steroid and immunosuppressant's in one and a repeat single dose of Rituximab in other.

While short term efficacy has been demonstrated in many case series the long term clinical course of pemphigus patients treated with rituximab are under assessment. Our patients have now been followed up for 6 years. An interesting research study by Colliou et al suggests that B-cell repertoire is reshaped after rituximab therapy



Case 1...Figures 1-3
Case 2...Figures 4-6
1, 4. Pemphigus vulgaris at presentation
2, 5. After 4 weeks of rituximab therapy
3, 6. After 11 weeks of rituximab therapy

Table 2 Patient Characteristic.

Sr.No	Gender/ Age(Y)	Diagnosis	Disease duration in Years	Previous Treatment	Concomitant therapy	TDC (w)	TCR(w)	Result
1	F/42	PV	8	MPD	None	4	12	CR (off)
2	F/43	PV	3	PD, CYC	AZP	3	12	CR (on)
3	M/33	PV	2	PD, CYC	None	5	16	CR (off)
4	M/31	PV	3	PD	AZP	4	20	CR (on)
5	F/58	PV	12	PD, MMF	None	5	16	R/CR (off)
6	M/36	PV	6	PD	None	3	16	CR (off)
7	F/36	PV	5	PD	AZP	5	16	CR (on)
8	F/44	PE	4	MPD, AZP	AZP	5	12	R/CR (on)
9	M/39	PF	3	MPD, AZP	None	3	8	CR (off)
10	F/31	PV	2	DCP, AZP	AZP	5	12	CR (on)

CYC: Cyclophosphamide; DCP: Dexamethosone cyclophosphamide pulse; F: Female; IVig: Intravenousimmunoglobulins; M: Male; MMF: Mycophenolatemofetil; MPD: Methylprednisolone; OFF: Offtherapy; ON: Ontherapy; PE: Pemphiguserythematosus; PD: Prednisolone; PV: Pemphigusvulgaris; R: Relapse; SrNo: Serial number; TCR: Time for complete remission; TDC: Time to disease control; W: Weeks; Y: Year.

allowing for long term effects in addition to the short term loss of pathogenic B cells^[8]. The authors followed up pemphigus patients from their early trial out at least 6 years after rituximab therapy. They found that nearly two thirds of patients achieved long term response either completely off therapy or when treated with low levels of supplementary prednisolone. They then compared patients with complete response to those with incomplete response to look at the differences in reconstitution of the B-cell compartment. In patients with complete remission they observed.

1. An increase of CD19+CD27-naïve B lymphocytes.
2. A decrease of CD19+CD27+memory B lymphocytes resulting in a marked and long lasting change of the naïve/memory B-cell ratio after rituximab treatment.
3. The expansion of transitional B-cells.
4. The expansion of IL-10 secreting regulatory B cells.

Complete responders had a specific loss of anti desmoglein specific B cells which are pathogenic in pemphigus patients but not B-cells that respond to infectious agents.

All patients who relapsed had either persistently high ELISA values of anti desmoglein or a reincrease of corresponding antibodies before the relapse. The persistent secretion of antidesmoglein IgG antibodies might be attributable to the long lived plasma cells or to the non-circulating long lived memory IgG + B cells which transform to plasma cells and are not targeted by anti CD 20 Therapy. This recurrent and/or new expansion in the B-cell repertoire explains non responders.

Ahmed et al too have reported durable remission upto 10 years in 10 patients of pemphigus treated with 10 infusions of rituximab over 6 months along with IVIG without any adverse effects^[9,10].

Baring issues regarding financial constraints, experience with rituximab validates its use as a first line treatment for pemphigus. This study attempts to add on to the experience of the efficacy of differing doses of rituximab in the treatment of pemphigus. Long term therapy of 7 months of rituximab gave prolonged remission without adverse events.

The limitations of our study include the retrospective design, the small number of patients with disease entities other than pemphigus vulgaris and the non-quantification of disease severity and immunologic factors before and after treatment.

Despite these limitations the study provides information specifically on the use of a modified lymphoma protocol providing sustained remissions in Indian patients from the western zone.

CONCLUSION

The use of biologic drugs in the treatment of pemphigus is yet in its evolution.

The use of anti CD 20 Antibodies biologic drugs in pemphigus is on the ascendant in India. Coming years will demonstrate use of differing dose regimens and long term results of the same. Ours is a preliminary study in an endeavor to achieve a fixed, safe, optimum, dosing schedule for rituximab in pemphigus. More number of such studies are warranted to support our view.

Thus, a protocol that is unique and optimum for autoimmune muco-cutaneous blistering disorders is the need of the hour.

REFERENCES

1. Huang A, Madan RK, Levitt J. Future therapies for pemphigus vulgaris: Rituximab and beyond. *J Am Acad Dermatol* 2016; **74**: 746-53.
2. Ahmed AR, Shetty SA. Comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. *Autoimmune Rev* 2015; **14**: 323-331.
3. Kanwar AJ, Vinay K. Rituximab in pemphigus. *Indian J Dermatol Venereol Leprol* 2012; **78**: 671-676.
4. Kanwar AJ, De D. Pemphigus in India. *Indian J Dermatol Venereol Leprol* 2011; **77**: 439-341.
5. Murrel DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori L, et al. Consensus statement on definitions of disease, endpoints and therapeutic response for pemphigus. *J Am Acad Dermatol* 2008; **58**: 1043-6.
6. Sharma VK, Bhari N, Gupta S, Sahni K, Khanna N, Ramam M, et al. Clinical efficacy of rituximab in the treatment of pemphigus: A retrospective study. *Indian J Dermatol Venereol Leprol*. 2016; **82**: 389-94.
7. Londhe PJ, Kalyanpad Y, Khopkar US. Intermediate doses of rituximab used as adjuvant therapy in refractory pemphigus. *Indian J Dermatol Venereol Leprol* 2014; **80**: 300-5.
8. Colliou N, Picard D, Caillot F, et al. Long term remission of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. *SciTransl Med*. 2013; **5(175)**: 175ra30.
9. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **335**: 1772-9.
10. Ahmed RA, Kaveri S, Spigelman Z. Long-term remissions in recalcitrant pemphigus vulgaris. *N Engl J Med* 2015; **373**: 2693-2694f