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Review Article

Rituximab in Pemphigus Vulgaris Patients: A Four-Year Clinical Experience Case Series Study from a Single Tertiary Care Center

Iman Almasry[1*], Jihan Rajy[1], Nadia Alnaki[1], Atlal Allafi[1]

[1]As'ad Al Hamad Dermatology Center, Shuwaikh Medical, Kuwait

***Correspondence author:** Iman Almasry, As'ad Al Hamad Dermatology Center, Shuwaikh Medical, Kuwait; Email: emmyms25@yahoo.com

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Abstract

Background: Pemphigus is a chronic debilitating autoimmune mucocutaneous disease. Pemphigus Vulgaris (PV) is one variant of many pemphigus types. Treatment of PV is challenging due to its complex nature, chronicity, as well as, the complications encountered with the medications used for its treatment. Recently Rituximab (RTX), a monoclonal antibody against the CD20, has been approved for the treatment of P.V in adults.

Objective: To analyze safety and efficacy of RTX infusion in PV patients.

Methods. Total patients in the study are 11. The studied patients were already established on systemic steroids and immunosuppressive, when rituximab was added to their treatment protocols. Rituximab was administered using a fixed-dose protocol 1 g intravenously on days 1 and 15 initiation dose.

Results: Eleven (seven males and four females) pemphigus vulgaris. Total duration of RTX treatment ranges from 12 to 46 months with a mean 20.33 ± 9.36 months.

All patients have shown clinical improvement on RTX infusion, two (18.18%) patients achieved complete remission off conventional therapy (steroid and immune-suppressive) in a mean duration of 17.5 months, six patients (54.5%) patients achieved complete remission on conventional therapy over a mean time of 7.6 months. The reported adverse effects were minor in 10 patients inform of low-grade fever temperature (37.6°C to 37.9°C), chills, body aches, nausea, diarrhea; and headache and cold symptoms (stuffy nose, sneezing and sore throat) all were transient and disappeared a few days after finishing infusion.

Conclusion: RTX infusion therapy acts to downregulate the desmogleins autoantibodies prevents propagating PV disease. RTX therapy is considered safe in patients with past autoimmune disease, cardiac disease and in patients with latent TB (after taking anti tuberculosis prophylactic treatment).

Keywords: Pemphigus Vulgaris; Desmogleins 1 and 3 (IgG 1, IgG3); Rituximab (RTX)

Introduction

Pemphigus is a chronic debilitating autoimmune mucocutaneous disease. Pemphigus Vulgaris (PV) is one variant of many pemphigus subtypes and it is a fairly rare disease that affects the skin and or mucous membranes. The skin blistering and mucosal erosions or ulcerations resulting from targeting IgG autoantibodies against; desmogleins 1 and 3 (IgG 1, IgG3) types [1]. This Initiate painful skin lesions (Bullae and erosions) which usually spread to involve an extensive body surface area in severe forms of PV. The severity of PV is correlated with the levels of serum desmogleins1,3 (IgG 1, 3) reactive autoantibodies [2]. Treatment of PV is challenging due to its complex nature, chronicity, as well as, the complications encountered with the medications used for its treatment. For many decades systemic steroids and steroid sparing immunosuppressive drugs, such as azathioprine, Mycophenolate Mofetil (MMF) or cyclophosphamide have been used for control of PV [3]. Recently Rituximab (RTX), a monoclonal antibody against the CD20, has been approved for the treatment of adults with moderate-to-severe PV and is increasingly being used as its first-line treatment [4]. Currently there is extensive evidence for the high efficacy and favorable safety profile of RTX in pemphigus patients with cutaneous, mucosal and mucocutaneous involvement [5].

Plan of the Study

Our study is case series observational study for some cases of our pemphigus vulgaris patients who haves received rituximab therapy over a period four years from January 1st, 2020 till December 31st, 2024. The patients' baseline characteristics; disease duration, clinical presentations, mucosal involvement, disease-severity assessment and adverse events with rituximab had documented during study and with regular follow up of patients. The total number of studied cases was 11, those who had received RTX therapy in addition to their conventional treatment after failure to achieve clinical and immunological remission. These patients have been followed for many years and have been adherent to an established treatment protocol in our Immune-Bullous Dermatology Clinic (IBDC) [6]. The total number of patients are eleven; all are registered in our IBDC with archived files. The demographic data and co-morbidities of patients were collected from their respective files. Severity scoring of the disease was assessed using pemphigus vulgaris activity score PVAS [7]. PVAS score was assessed at the base line and at a 3 months interval till clinical remission. Immunological remission was assessed through indirect IIF and Anti-Desmoglein (Dsg) 1,3 titers at baseline, every 3 months till immunologic remission after starting RTX infusion.

The studied patients were already established on systemic steroids and immunosuppressive, when rituximab was added to their treatment protocols. All patients were investigated prior to starting rituximab, with basic lab work up (CBC, liver and renal functions), Electrocardiogram (ECG), Mantoux test for latent TB (Latent Tuberculosis) and chest X-ray and a serology for viral hepatitis screening. 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 protocol 1 g intravenously on days 1 and 15 initiation dose and subsequent booster dose of 500 mg after 6 to 12 months according to patients' response. All patients were admitted to our inpatient department and were monitoring over a period of 5-6 hours during RTX infusion and for an additional 24 hours after completion. Patients received pre-infusion medications inform of hydrocortisone 100 mg IV (as methylprednisolone was not available), diphenhydramine 50 mg IV and oral paracetamol 500 mg 30 and 60 minutes respectively before infusion. All adverse effects experienced by the patients were reported during and after infusion of rituximab. Patients were evaluated at monthly intervals for a minimum of six months and then every 3 months with immunology tittering. Patients were kept on their previous treatments (systemic steroids and immunosuppressants) and the dosage of each were evaluated according to clinical and immunologic remissions.

Results

Eleven (seven males and four females) pemphigus vulgaris patients were included in the study. All clinical and immunological features of studied patients are seen in (Fig. 1, Table 1).

		Age	Duration	PVAS	Dsg1b	Dsg3b	Dsg1 be	Dsg1 af	BMI	CRp/on	CRt/off	Dt	PVASaf
N	**Valid**	11	11	11	11	11	11	11	11	2	3	11	11
	Missing	0	0	0	0	0	0	0	0	9	8	0	0
Mean		46.45	7.727	6.0500	69.1691	158.0573	42.664	9.164	25.691	17.500	15.333	20.273	0.982
Std. Deviation		11.961	4.7977	4.77530	75.54060	43.28448	59.7004	18.3179	4.4646	0.7071	2.5166	9.3605	2.5872
Minimum		32	1.0	2.00	0.00	99.40	0.0	0.0	18.5	17.0	13.0	12.0	0.0
Maximum		70	16.0	16.00	203.20	224.60	197.8	52.5	33.1	18.0	18.0	46.0	8.5
Percentiles	25	37.00	4.000	2.5000	0.0000	108.0000	0.000	0.000	22.500	17.000	13.000	14.000	0.000
	50	45.00	7.000	4.5000	65.0000	151.7000	28.800	0.000	27.300	17.500	15.000	18.000	0.000
	75	54.00	13.000	9.1000	118.7000	198.3000	68.100	10.800	28.900			23.000	0.000

PVAS: Pemphigus Vulgaris Activity Score, Dsgb1,3: Desmogleins1,3base Iine, Dsgaf1,3: Desmogleins1,3 After RTX infusion, BMI: Body Mass Index, CRp/on: partial Clinical Remission on conventional therapy/off: complete clinical remission off conventional therapy

Table 1: Main clinical and immunological features of study's patients.

The age of these patients ranged from 32 to 70 years, with a mean of 46.45 ± 11.96 years. There were 10 (90.90%) patients with mucocutaneous presentation and 1 patient (9.10) had mucosal affection only. The PAVS score at baseline ranging from 2 to 16 with a mean of 6.05 ± 4.77 (Table 2). Three of patients were found to have latent T.B as their chest X-ray was normal but with positive TB test. These three patients had been given prophylactic antituberculosis treatment through pulmonary physician for 9 months according to their guidelines for prophylaxis before starting RTX infusion.

Total duration of RTX treatment ranges from 12 to 46 months with a mean 20.33 ± 9.36 months. All patients have shown clinical improvement on RTX infusion, two (18.18%) patients achieved complete remission off conventional therapy (steroid and immune-suppressive) in a mean duration of 17.5 months, six patients (54.5%) patients achieved complete remission on conventional therapy over a mean time of 7.6 months. The remaining three patients (27.27%) have achieved partial remission over a mean time of 15.33 months (13 to 18 months). Two patients who achieved only partial remission had shown a resistant vegetative plaque for which intralesional triamcinolone acetate 10 mg/ml was administered twice, two weeks apart with complete resolution of scalp and partial improvement of gluteal skin lesions (Fig. 1,2) consecutively, the latter patient has high BMI (33.1). There was reduction in PAVS after RTX range (From 2 to 16) with mean 6.05 ± 4.77 to become range 0 to 8.5 with mean 0.982 ± 2.58 which was statistically significant to baseline PAVS ($P < 0.05$). Immunologically there was a highly significant correlation after RTX treatment ($P < 0.001$), IIF became negative in two, while in 6 pt their DsG1 and 3 pt with DsG3 later became negative post RTX treatment in a mean time of 20.27 months. The conventional treatments (systemic steroids and immunosuppressive medications) were maintained for all patients with gradual reduction in dosage. RTX 500 mg was given as a maintenance dose after 6 months or 12 months if no clinical and immunological remission. Total RTX cycles to achieve clinical remission was 4 in average on/off conventional therapy, three patients had achieved complete clinical remission off treatment without relapse till clinical end of our study.

Total number of patients = 11	
Characteristics of pemphigus patients	
Sex	
Male	7 (63.63)
Female	4 (36.36)
Age (Mean, range)	46.45± 11.96 (32 to 70)
Pemphigus vulgaris	
Skin/ mucous membrane	10 (90.90)
Mucous membrane.	1 (9.10)
Baseline PVAS (Mean, range)	6.05± 4.77 (2 to 16)

Table 2: Patients' characteristics.

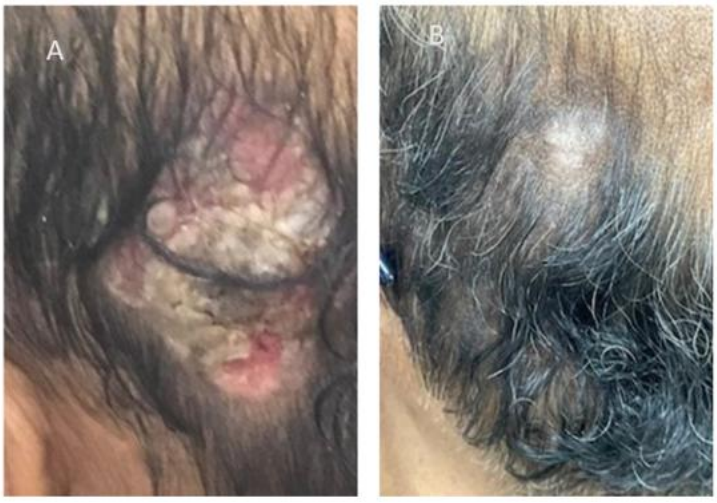

Figure 1: a: Male patient 34 years shows active vegetative skin lesion over left partial scalp before RTX. Infusion; b: Shows complete resolved skin lesion, 9 months after RTX. Infusion.

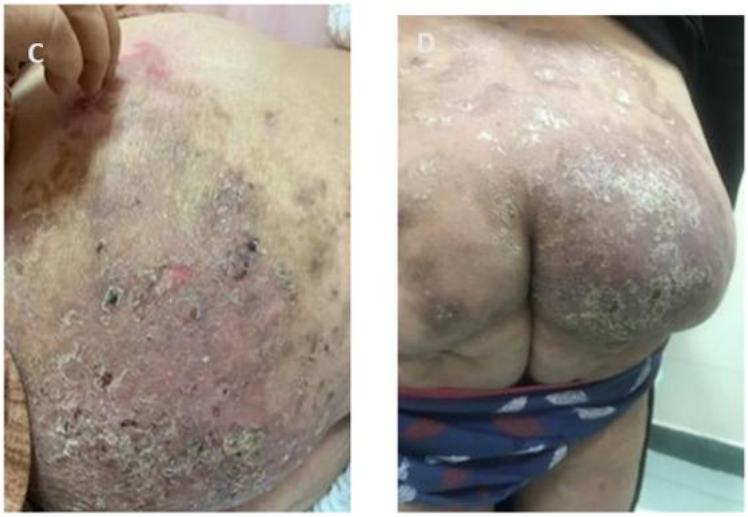

Figure 2: a: Female patient 70 years shows large active skin erosion over right buttock before RTX. Infusion; b: Patient shows partial remission 18 months after RTX infusion.

The reported adverse effects were minor in 10 patients inform of low-grade fever temperature (37.6°C to 37.9°C), chills, body aches, nausea, diarrhea; and headache and cold symptoms (stuffy nose, sneezing and sore throat) all were transient and disappeared a few days after finishing infusion. Only one patient (Female 70 years with multiple comorbidities) developed shortness of breath and palpitation during the first cycle of RTX. She was managed by the physicians and discharged after her condition stabilized within 24 hours of infusion. She tolerated her next RTX infusions without any further serious adverse effects. Rituximab was safe in all patients regardless their medical history or associated comorbidities including metabolic syndrome (dyslipidemia, DM and HTN), atherosclerotic heart disease and coronary stents (Table 3). One male pt with past history of autoimmune disease of viral encephalitis, patients tolerated RTX well without any significant adverse effects during or after completion of RTX treatment. Patients who had latent T.B did not show activation during infusion.

Pts.No	Comorbidities /Past history
3	Non
1	Dyslipidemia
1	Dyslipidemia ,HTN
1	Dyslipidemia, DM
1	DM,HTN
1	Dyslipidemia, HTN , pulmonary embolism
1	HTN, DM ,ischemic heart dis. ,cardiac stent
1	Viral encephalitis
1	Primary infertility ,PCO

Table 3: Comorbidities for studied patients.

Discussion

Rituximab is a chimeric monoclonal antibody specific for CD20, was initially approved by the FDA for the treatment of non-Hodgkin's lymphoma and rheumatoid arthritis [8,9]. Over the past years RTX was used off-label in immune-bullous diseases, especially in recalcitrant PV and paraneoplastic pemphigus for which it demonstrated its efficacy and safety [10-12]. Few years back the FDA and the European Commission approved the use of rituximab for the treatment of patients with moderate to severe PV [13,14]. In our study eight (72.68 %) patients showed complete CR and IR remission (Three patients off and five patients on conventional therapy) and three patients achieved partial CR with a mean time of 15.33 months; our result is comparable with previous studies done [15,16]. A statistically significant reduction of PAVS ($P < 0.05$) from baseline and after RTX infusion was shown, with a mean time of 17.5 months without relapse in patients with complete remission till end of our study. This is comparable with another retrospective study [16]. Six of the studied patients achieved immunological remission of DsG1 and DsG3, which was highly significant ($P < 0.001$) after RTX infusion in mean time 20.27 months which was nearly the same in study [17]. All our patients were complete or partial responders clinically and immunologically; which was documented in other study [18]. The patients who achieved complete clinical and immunological remission, did not have any relapse till the end of our study within the 48 months duration of the study and was longer than previous studies averaging 24 months following rituximab infusion [19]. Regarding the safety profile of RTX, no serious adverse effects were reported in 10 patients which is similar to another documented results [20]. One patient had experienced a serious infusion reaction after her first cycle of RTX but did not experience any reactions in her following infusion cycles. Infusion related reactions were reported in 5.9% of patients [21]. In addition, no activation to latent TB in patients with after they received prophylactic treatment before starting RTX Patients. The previous treatment with steroid and immunosuppressive drugs had been reduced to more than half their respective dosages to the baseline starting dose after RTX infusion. Patients who had shown downregulation for IIF and Dsg1 and 3 antibodies titers on previous systemic steroid and immunosuppressive have achieved complete immunological remission after RTX infusion, this is in keeping with previous study [22].

Limitation

The main limitation of our study was the small sample size and the lack of a comparison group.

Conclusion

Importantly this study demonstrated a strong additional therapeutic efficacy of RTX in patients with PV who are receiving the conventional steroid and immunosuppressive treatments. RTX infusion therapy acts to downregulate the desmogleins autoantibodies prevents propagating P.V disease. So, RTX translates to better P.V control with an additional possibility of decreasing the dosage of the conventional medications used in PV treatment and thus their adverse side effects. RTX therapy is considered safe in patients with past autoimmune disease, cardiac disease and in patients with latent TB (after taking anti tuberculosis prophylactic treatment). Although RTX has been licensed for treatment in PV, more studies are needed to provide an optimal protocol for rituximab treatment and discover new or possible markers for predicting improvement in the management of pemphigus patients. Rituximab is considered standard treatment in addition to the conventional therapy for P.V.

Conflicts of Interest

The authors declare no conflict of interest in this paper.

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None

Authors' Contributions

All authors contributed to conceptualization, treatment execution, manuscript writing and final approval.

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