Evaluation of the efficacy and safety of rituximab in patients with refractory pemphigus vulgaris

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Background: Recently, rituximab has been successfully used for the treatment of pemphigus family, the main subtype of which is pemphigus vulgaris (PV). The aim of this study was to determine the efficacy and safety of rituximab in refractory PV.

Methods: In an observational study extending from November 2014 to February 2016, 30 patients with refractory PV were treated with rituximab. Response to therapy, duration of clinical remission, relapse rate, serology, and side effects of treatment with rituximab were evaluated.

Results: At the end of the follow-up with a mean duration of 7.6 (6-14) months, 25 (83.3%) patients achieved complete remission with or without systemic therapy. The mean duration of disease control was 2.8 months. In all patients, the serum levels of anti-desmoglein 1 and 3 IgG antibodies were reduced after rituximab therapy. In 23.4% of the patients, a clinical relapse occurred at a mean of 9.6 months following the initiation of the treatment. Infusion-related reactions occurred in 18 (60%) patients. The lack of a control group, concomitant use of corticosteroid and immunosuppressive agents, and a limited follow-up period were among the limitations of our research.

Conclusions: Rituximab is a good treatment modality for refractory PV, which extends the mean time to relapse in patients. To further extend our knowledge on the efficacy and safety of rituximab therapy, more randomized controlled trials with larger sample sizes and prolonged follow-up durations are required.

Keywords: rituximab, pemphigus vulgaris, desmoglein, refractory

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INTRODUCTION

Pemphigus vulgaris (PV) is the main subtype of pemphigus group with potentially fatal outcomes mediated by autoantibodies against desmoglein 1 (Dsg. 1) and desmoglein 3 (Dsg. 3), adhering molecules of the epidermal and external mucosa, respectively [1].

To date, the first line of treatment is systemic corticosteroids (CS), alone or in combination with immunosuppressive agents. Theses conventional treatments ensue serious side effects, morbidity and mortality, both in PV and other dermatologic diseases [2-6].

Recently, rituximab has been successfully employed in the treatment of pemphigus group. This medication is a chimeric murine/human monoclonal antibody directed against the CD20 antigen expressed on B lymphocytes. One of the several mechanisms of rituximab is B-cell-cytolytic activity, mainly through antibody-dependent cell-mediated cytotoxicity [7-10].

Although the efficacy and safety of rituximab in refractory PV have been shown in recent studies,

the likelihood of prolonged complete remission is yet to be elucidated.

The objective of this study was to assess the efficacy and safety of rituximab therapy in Iranian patients with refractory PV.

PATIENTS AND METHODS

The protocol of the study was performed according to the Declaration of Helsinki and approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran. Informed consent was sought from the patients according to legal requirements.

In an observational study which lasted from November 2014 to February 2016, we enrolled a total of 30 patients with severe or refractory PV treated with rituximab. All patients had been diagnosed with PV by clinical, histopathological and immunofluorescence features. All subjects had received conventional treatments including methylprednisolone pulse therapy, azathioprine (1-2mg/kg/day), mycophenolate mofetil (2000mg/day), dapsone (100mg/day), cyclophosphamide (1-2mg/kg/day) and/or prednisolone (0.5 -1 mg/kg/day).

Exclusion criteria were history of hypersensitivity to murine proteins, cardiovascular or pulmonary diseases, any malignancy, (Hepatitis B Virus) HBV carriers, active and/or severe infections, pregnancy and breastfeeding.

The severity of PV was assessed according to revised severity index for pemphigus vulgaris without antibody titre by Ikeda et al. [11] and included four items:

1. Percentage of skin involvement in relation to total skin surface area (0: none; 1: <5%; 2: 5%-15% and 3 :> 15%).
2. Oral lesion defined as the percentage of involved area in relation to the total mucous membrane surface area (0: none; 1: <5%; 2: 5%-30% and 3: >30%).
3. Nicolsky phenomenon (0: none; 1: only focal; 2: positive and 3: distinct).
4. Number of new lesions per day (0: none; 1: occasional; 2:1-5 blisters; 3: <15 blisters).

The sum of the scores gives the severity index and is regarded as mild if <5, moderate if 5-7 and severe if higher than 7 [11].

All cases received rituximab (at least 1 cycle infusion of 375 mg/m²/week for 4 consecutive weeks) if they had one of the following criteria:

1. Contraindication or lack of response to conventional therapies.
2. Two relapses during the gradual tapering of treatment dosage.

Clinical response to treatment with rituximab was classified based on the consensus statement.

- Complete remission off therapy (CR-off therapy): The absence of new or stable lesion while the patient is off all systemic therapies for at least 2 months.
- Complete remission on minimal therapy (CR- minimal therapy): The absence of new or stable lesion, while the patient is receiving minimal therapy.
- Partial remission off therapy (PR-off therapy): The presence of transient lesions that heal within a week without treatment, while the patient is off all systemic therapies for at least 2 months.
- Partial remission on minimal therapy (PR-minimal therapy): The presence of transient lesions that heal within 1 week without treatment, while the patient is receiving minimal therapy including prednisolone (or the equivalent) at ≤ 10mg/d and/or minimal adjuvant therapy and/or topical corticosteroid for at least 2 months.
- Relapse: The appearance of ≥ 3 new lesions per month that do not heal spontaneously within 1 week or the extension of established lesion [12].

Anti-DSG-1 and anti-DSG-3 antibodies were measured prior to the initiation of rituximab therapy and at the end of the follow-up. Cut-off index was defined as 20 U/mL and the negative value was below 20 U/mL.

RESULTS

Thirty consecutive patients (22 females, 8 males) with PV were included in this study. The median age (range) at diagnosis was 39.7 (18-72) years, and the median disease duration before rituximab therapy was 6.5 (0-22) months. The clinical and immunologic characteristics of all subjects are detailed in Table 1. Mucous membrane involvement was found in 28 (93.4%) patients.

Table 1. Clinical and immunologic characteristics of patients with pemphigus vulgaris (before rituximab therapy).

Patient	Sex	Age (year)	Duration of disease (month)	Previous treatments	Anti Dsg.1 (U/mL)	Anti Dsg.3 (U/mL)
1	F	73	1	CS,AZA	155	3.2
2	M	55	20	CS, AZA, MMF, dapsone, IVIg	200	200
3	F	18	0	CS,AZA	0.3	0.7
4	F	44	15	CS	171.5	2.7
5	F	56	20	CS,AZA	1.9	200
6	F	48	18	CS,AZA,MMF	7.1	185.2
7	F	50	5	CS,AZA	3.6	2.5
8	F	33	1	CS,AZA	3.6	0.3
9	M	50	5	CS	3.1	200
10	F	46	0	CS,AZA	1.2	135.2
11	F	59	6	CS,AZA	5.6	200
12	M	48	3	CS, AZA, MMF, cyclophosphamide	1.8	200
13	F	39	8	CS, AZA, MMF, dapsone	15.1	23.2
14	F	47	5	CS,AZA,MMF	0.2	0.7
15	M	29	1	CS,AZA	105	190
16	M	46	0	CS,AZA	21.1	5.2
17	F	40	14	CS,AZA,MMF	3.1	200
18	F	42	12	CS,AZA,MMF	125.6	35.1
19	F	36	10	CS,AZA	5.6	200
20	F	51	4	CS,AZA	3.9	200
21	F	35	1	CS,AZA	1.8	5.2
22	M	44	0	CS,AZA	3.1	6.5
23	F	67	2	CS	2.2	155
24	F	32	3	CS,AZA	9.7	80.4
25	F	42	2	CS,AZA	3.1	5.2
26	M	48	13	CS,AZA	5.6	200
27	M	52	22	CS,AZA,MMF	1.8	200
28	F	61	7	CS,AZA	1.8	23.5
29	F	45	6	CS,AZA	9.5	80.2
30	F	53	0	CS,AZA	19.1	17.2

AZA, azathioprine; CS, systemic corticosteroids; Dsg. 1, desmoglein. 1; Dsg. 3, desmoglein. 3; F, female; IVIg, intravenous immunoglobulins; M, male; MMF, mycophenolate mofetil

Pervious therapies included prednisolone (n=29), azathioprine (n=26), mycophenolate mofetil (n=8) and cyclophosphamide (n=1).

Clinical response

All patients received at least one complete rituximab cycle, comprised of four infusions of 375mg/m² at weekly intervals. The mean duration of follow-up after treatment was 7.6 (6-14) months. Six (20%) patients had CR and were off all treatments, 19 (63.3%) had CR and were on low doses of oral prednisolone and/or other immunosuppressants, one (3.3%) patient had PR and was off all treatments, four (13.3%) patients had PR and were on low doses of prednisolone (Table 2). The mean duration of disease control was 2.8 months.

Relapse

Clinical relapse occurred at a mean of 9.6 months following the initiation of rituximab therapy. Four (16.7%) patients received one additional rituximab infusion, and two (6.7%) cases received a high dosage of CS and immunosuppressive agents for the disease control. Patients who immediately relapsed following the gradual reduction in CS dosage (to less than 10 mg/day), experienced no recurrences during the follow-up period after rituximab therapy.

Patient follow-up

Serum levels of anti-DSG-1 and anti-DSG-3 IgG antibodies were evaluated for all cases at the baseline and at the end of the follow-up period. The mean of anti-DSG-1 titre was 29.73 at the baseline

Table 2. Clinical and immunologic status of patients treated with rituximab at the end of follow up period.

Patient	Concomitant therapy	Adverse events	Clinical outcome	Relapse, no.	Time to clinical improvement (months)	Anti Dsg.1 (U/mL)	Anti Dsg.3 (U/mL)
1	CS,AZA	Orthostatc hypotension	CR (on)	1	2	108.5	2.6
2	CS,MMF	none	CR (on)	1	2	170.3	9.3
3	CS,AZA	flushing	CR (on)	0	1	0.1	0.3
4	none	dyspnea	CR (off)	0	4	108.5	1.2
5	CS	flushing	CR (on)	0	3	0.7	50.7
6	CS,MMF	none	PR (on)	1	4	1.3	108.6
7	CS	none	CR (on)	0	2	1.2	1.9
8	none	flushing	CR (off)	0	2	0.3	0.2
9	CS	none	CR (on)	0	1	2.8	40.9
10	CS,AZA	flushing, dyspnea	CR (on)	0	3	0.1	2.3
11	CS,AZA	none	CR (on)	0	1	1.2	103
12	CS,MMF	fever	PR (on)	0	6	1.2	108.5
13	CS,AZA	flushing, dyspnea	CR (on)	1	1	7.1	17.5
14	CS,MMF	fever	CR (on)	0	4	0.1	0.2
15	CS,AZA	None	CR (on)	0	1	28.5	8.4
16	CS,AZA	none	CR (on)	1	3	0.1	2.5
17	none	cough	CR (off)	0	1	1.7	34.4
18	none	none	CR (off)	0	2	14.9	2.8
19	CS	none	CR (on)	0	5	0.1	105.2
20	CS,AZA	none	CR (on)	0	1	1.9	112.5
21	CS,AZA	Sinus tachycardia	CR (on)	0	2	0.1	1.2
22	CS,AZA	none	PR (on)	0	3	1.4	1.3
23	none	none	CR (off)	0	4	0.7	5.9
24	CS,AZA	dyspnea	CR (on)	1	4	3.9	18.3
25	CS,AZA	Orthostatic hypotension	CR (on)	0	4	0.1	0.1
26	CS,AZA	none	CR (on)	0	3	1.3	104
27	CS,AZA	none	CR (on)	0	4	1.2	105.2
28	CS,AZA	none	PR (on)	0	5	0.1	2.5
29	none	dyspnea	PR (off)	0	5	3.4	18.2
30	none	flushing, dyspnea	CR (off)	0	1	8.2	1.6

AZA, azathioprine; CR (off), complete remission off treatment; CR (on), complete remission on treatment; MMF, mycophenolate mofetil; no, number; PR (off), partial remission off treatment; PR (on), partial remission on treatment

and 15.7 at the end of follow-up. The mean of anti-DSG-3 titre was 98.57 at the baseline and 32.37 at the end of follow-up. The autoantibodies titres decreased after rituximab therapy, indicative of clinical improvement ($P<0.05$). Prior to rituximab therapy, anti-DSG-1 and anti-DSG-3 antibodies were positive for 6 and 19 patients, respectively. Following rituximab therapy, the serum levels of these two antibodies returned to normal in 3 and 9 patients with positive anti-DSG-1 and anti-DSG-3, respectively.

Adverse events

All cases tolerated treatment with rituximab during infusion. Infusion-related reactions occurred in 18 (60%) patients, including fever, flushing, dyspnea, cough, orthostatic hypotension and sinus tachycardia, where rituximab was administered at a slower rate. No serious adverse events were observed.

DISCUSSION

Our study evaluated the efficacy and safety of rituximab therapy in 30 Iranian patients with refractory PV. B lymphocytes are targeted by rituximab, an anti-CD20 chimeric monoclonal antibody that does not target plasma cells and stem cells due to the lack of CD20 on the surface of the cells[13-15]. In a review conducted by Avivil et al., B cell, serving as antigen-presenting cells, was found eliminated, thereby causing impaired T cell activation. They further reported a significant reduction in IFN-γ-secreting T cell (Th1) and Dsg3-specific IL-4- secreting T cell (Th2) [16].

Two treatment protocols are, more often than not, employed in the treatment of pemphigus: the lymphoma protocol (375mg/m²/week administrated four times) and the rheumatoid arthritis protocol (two infusions of 1 gr, administrated 2 weeks apart) [17].

In our study, patients were treated according to the lymphoma treatment protocol, and the concomitant systemic medications during rituximab therapy were prednisolone, azathioprine and mycophenolate mofetil.

In a review conducted by Kasperkiewicz et al., 61% complete remission was achieved in rituximab-treated PV patients, in accordance with.our study, where 83.3% achieved complete remission [3].

In the present research, 6 out of 30 patients experienced relapse, which is close to that reported by Heelan et al. [18] Four of our 6 relapsing patients were successfully treated with an additional rituximab cycle, and two were treated with a high dose of CS or classic immunosuppressants.

Anti-DSG-1 and anti-DSG-3 antibodies were positive for 6 and 19 cases, respectively, and their titres were paralleled with the clinical phenotype. However, after rituximab therapy, Anti-DSG-1 and anti-DSG-3 titres decreased significantly from the baseline to the end of the follow-up, while 33% and 13.3% of the subjects still had ELISA detectable Anti-DSG-1 and anti-DSG-3 antibodies, respectively. Consistent with our results, Kwon et al. found that 46.5% of cases with PV and 33.3% of cases with pemphigus foliaceus were Anti-DSG-1 and anti-DSG-3 ELISA positive, respectively [19]. However, in line with the present study, Anti-DSG-1 and anti-DSG-3 titres were always lower than the baseline values. Abasq et al. showed that the clinical responses following rituximab therapy in pemphigus do not always correlate with the changes in the serum levels of autoantibodies [20].

Rituximab therapy has been associated with several side effects, most of which occur during infusion and include fever, chills, dyspnea, flushing, pruritus and orthostatic hypotension [18].

In a review done by Peterson et al, 7 out of 71 patients had severe life-threatening infections, along with many confounding factors such as previous and/or concurrent use of immunosuppressive agents, underlying medical conditions like cancer and diabetes mellitus which had made them more susceptible to infections [13]. In the current study, all patients were screened for hepatitis B and C viruses, and human immunodeficiency virus prior to rituximab therapy. No serious infections were observed either during treatment or at the end of follow-up.

Further studies are required to determine whether the increase in the risk of infection is related to treatment with rituximab, immunosuppressive therapy or other underlying diseases.

The lack of a control group, concomitant use of CS and immunosuppressive agents, and a limited follow-up period were among the limitations of our research.

The findings of previous studies along with those of our study show that rituximab is a good treatment modality for refractory PV, and, interestingly, we found that this treatment is able to extend the mean time to relapse in these patients. Nonetheless, more randomized controlled trials with larger sample sizes and prolonged follow-up durations are required to clarify the efficacy and prolonged safety of rituximab therapy in PV.

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