Erciyes Med J 2021; 43(3): 267–72 • DOI: 10.14744/etd.2020.82356
ORIGINAL ARTICLE – OPEN ACCESS

Efficacy and Safety Data for Rituximab (Anti-CD20) in the Treatment of Pemphigus Vulgaris: A Retrospective, Single-Center Study

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ABSTRACT

Objective: The aim of the study was to evaluate the efficacy and safety of rituximab treatment in patients with pemphigus vulgaris.

Materials and Methods: Seventeen patients who received rituximab treatment with the diagnosis of pemphigus vulgaris were included in the study. Rituximab was administered according to rheumatoid arthritis protocol. The patient demographic and clinical information, disease duration, previous treatments, additional diseases, disease course after rituximab, and side effects were evaluated retrospectively by scanning patient files.

Results: The average age of patients was 49.1±12.1-years-old. In 3 (17.6%) patients, the drug regime could not be completed due to the reaction that developed during the infusion. One of the 14 patients who were treated could not be followed up due to exitus. Complete remission occurred in all 13 patients who were followed up, and the median duration of complete remission was 4.2 months (min: 2, and max: 13 months); however, 6 (45.1%) patients relapsed within an average of 11±3.7 months. Examination of the pemphigus disease area index (PDAI) scores shows that the pre-rituximab values in the 13 patients were between 12 and 65 (mean 28.6±15.9), while those in 12 patients were zero at the past follow-up, with only one patient's PDAI value being calculated as 20. As side effects, infusion reaction in three patients, lymphopenia in five patients, herpetic keratitis in one patient, cerebritis, sepsis, and death due to intracranial hemorrhage occurred in one patient.

Conclusion: It can be concluded that rituximab treatment was effective in pemphigus vulgaris; however, it is necessary to be careful in terms of side effects such as lymphopenia and infection.

Keywords: Efficacy, pemphigus, rituximab, safety, treatment

Cite this article as:
Solak EÖ, Gökçek GE, Çınar SL, Kartal D, Borlu M. Efficacy and Safety Data for Rituximab (Anti-CD20) in the Treatment of Pemphigus Vulgaris: A Retrospective, Single-Center Study. Erciyes Med J 2021; 43(3): 267-72.

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Submitted
05.11.2020

Accepted
27.11.2020

Available Online
05.04.2021

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INTRODUCTION

Pemphigus is a group of autoimmune, chronic, and bullous diseases that can involve the skin and mucous membranes; it can sometimes result in death. Autoantibodies, mainly of the IgG structure, bind to desmoglein-1 and/or desmoglein-3, which are epidermal adhesion molecules, causing acantholysis and the development of bulla (1). The most common disease in this group is pemphigus vulgaris (2), the incidence of which varies according to ethnic origin and geographical region. In Europe, the annual incidence varies from 0.5 to 4.0/million (3), and it has been reported as being 2.4/million in a study involving the Mediterranean region of Turkey (4). While pemphigus is common in European countries between the ages of 50 and 60, it can be seen in younger ages (3). Pemphigus vulgaris is a disease that can be fatal if left untreated, and the main purpose of treatment is to induce and maintain remission; corticosteroids are the basis of therapy. Following the introduction of steroid therapy in the early 1950s, the mortality rate decreased from 70% to 30%, and the use of immunosuppressant drugs as adjuvants since the 1980s has reduced this rate to <5% (5). However, relapse is seen in approximately 50% of patients and serious adverse events related to immunosuppressants in roughly 65% (1) have encouraged the research and development of novel therapies for pemphigus in recent years.

Rituximab is a monoclonal antibody against the CD20 antigen found on B lymphocytes that remove CD20+ B cells from the circulation for approximately 6–12 months and was first used in the treatment of pemphigus vulgaris in 2002 (6). Although rituximab has been used in resistant pemphigus and patients suffering serious side effects to traditional immunosuppressive treatments, recent studies have highlighted the successful combined use of rituximab and prednisone as a first-line treatment for pemphigus (7).

In the present study, we aimed to retrospectively evaluate the efficacy and safety of rituximab treatment in patients with pemphigus vulgaris: Who were followed up at the Dermatology Department of Erciyes University; whose diagnosis was confirmed by clinical, histological, and/or immunopathological tests; and who could not achieve remission with systemic steroids and traditional immunosuppressive agents or had any contraindications to these treatments.

MATERIALS and METHODS

Seventeen patients who were followed up at Erciyes University Dermatology Department between 2012 and 2019 with a diagnosis of pemphigus vulgaris and deemed appropriate for rituximab treatment were included in the present study. Approval was obtained from Erciyes University Ethics Committee, No. 2020/247. The patient demographic and clinical information, disease duration, previous treatments, additional diseases, disease course after rituximab, and side effects were evaluated retrospectively by scanning patient files. All patients received rituximab treatment according to the rheumatoid arthritis protocol: Rituximab 1000 mg was administered twice with a 2 weeks interval following premedication with 100 mg intravenous methylprednisolone, one ampoule of intravenous pheniramine, and 1000 mg oral paracetamol. The treatment was repeated 6 months later, if required. The pemphigus disease area index (PDAI) was used to evaluate disease severity. The PDAI has a total score ranging from 0 to 263, of which 250 show disease activity and 13 show disease damage. The skin, mucosa, and scalp are divided into sections (12, 12, and 1, respectively), each of which is scored from 1 to 10; thus, the total score indicating activity ranges from 0 to 250 (8). In our study, we evaluated the disease severity of pemphigus using the PDAI activity score without including the damage score.

Definitions developed by an international panel of experts were used to evaluate treatment efficacy (9). According to this:

Controlled Disease Activation

When no new lesions form and existing lesions begin to heal.

Complete Remission without Treatment

No lesions in a patient who has not received systemic therapy for at least 2 months.

Complete Remission with Treatment

No new or existing lesions in the patient during receipt of minimal therapy.

Minimal Treatment

Prednisone (or equivalent) at a dose of 10 mg/day or less and/or minimal adjuvant therapy for at least 2 months.

Relapse

Occurrence of three lesions per month that does not heal spontaneously within 1 week or the enlargement of an existing lesion in a patient in whom the disease is controlled.

Statistical Analysis

The SPSS software (Statistical Package for the Social Sciences, 15.0 version; SSPS Inc, Chicago, Illinois, USA) was used for statistical analysis. The distribution of continuous variables was tested using the one-sample Kolmogorov–Smirnov test, and the data are presented as the mean value±standard deviation or median and minimum-maximum ranges. Categorical variables are reported as the frequency and group percentage.

RESULTS

Within the specified period, 26 patients with pemphigus vulgaris received rituximab treatment, 17 of whom met the criteria and were included in the present study: Ten (58.8%) were men and seven (41.1%) were women. Nine patients were excluded due to lack of data or scoring. The average age of the patients was 49.1±12.1-years-old. All patients had mucocutaneous-type pemphigus vulgaris. The disease duration varied from 13 to 252 months, with a mean of 88.5±62.9 months. All of patients were administered systemic steroid therapy with doses of 0.5–1.5 mg/kg for about 6–24 months for varying durations before the administration of rituximab, and at least one adjuvant agent was used. Accompanying diseases of patients together with pemphigus vulgaris and complications due to previous treatments are shown in Table 1 together with. While seven patients had no accompanying disease, one patient had tuberous sclerosis, two patients had asthma, one patient had hypothyroidism, three patients had hypertension, and two patients had diabetes. Mucosal Candida infection developed in all patients due to previous treatments. Steroid myopathy developed in two patients, osteoporosis developed in three patients, aseptic necrosis of the femoral head developed in two patients, cushingoid appeared in four patients, and hypertrichosis appeared in one patient (Table 1). During rituximab treatment, seven patients received additional intravenous immunoglobulin (IVIG) at the dose of 2 g/kg every month, one patient received additional IVIG + 100 mg methylprednisolone, one patient received additional 48 mg methylprednisolone, one patient received additional IVIG-mycophenolate mofetil, one patient received additional azathioprine 150 mg/day, one patient received additional mycophenolate mofety l–8 mg methylprednizalone, one patient received additional IVIG + 48 mg methylprednisolone, and four patients were not given additional treatment. In 3 (17.6%) patients, the drug regime could not be completed due to severe drug reaction during the infusion. One of the remaining 14 patients was out of follow-up due to sudden death after treatment. The remaining 13 patients were followed up for a median of 32 months (min: 19, and max: 99 months). The median time until disease control was 5 weeks (min: 4 weeks, and max: 8 weeks). In all patients, complete remission was achieved. The median duration of complete remission was 4.2 months (min: 2, and max: 13 months); during follow-up; however, 6 (46.1%) patients relapsed within an average of 11±3.7 months. Examination of the PDAI scores shows that the pre-rituximab values in the 13 patients were between 12 and 65 (mean 28.6±15.9), while those in 12 patients were zero at the past follow-up, with only one patient's PDAI value being calculated as 20. At present, 12 patients are in complete remission: Seven without any medication and five with IVIG. However, one patient relapsed as a moderately severe disease (8) and is being followed up with azathioprine as a side effect, three patients developed an infusion reaction which caused discontinuation of treatment. Lymphopenia was observed after rituximab treatment in five of the 14 patients who were treated and lymphopenia resolved spontaneously during follow-up, one patient developed herpetic keratitis (7.14%) during follow-up, one patient developed cerebritis, sepsis, and then exitus due to intracranial hemorrhage (7.14%). Other eight patients developed no side effects (Table 2).

DISCUSSION

Rituximab has been used in pemphigus vulgaris patients since 2002. In the randomized study, Ritux 3, it was reported that short-term prednisone use in conjunction with rituximab is more ef-

Table 1. Demographic and clinical characteristics of patients before rituximab treatment

Patient number	Age	Gender	Duration of disease (months)	Previous treatments	Side effects due to previous treatments	Additional diseases
1	50	Male	36	1,2,3,4	Myopathy	Tuberous sclerosis
2	21	Male	50	1,3	None	–
3	45	Male	70	1,2,3,4,5	Acneiform eruption	–
4	59	Female	95	1,2,3	Osteoporosis	Asthma, hypothyroidism
5	32	Male	144	1,2,3,4,5	Osteoporosis	–
6	39	Male	108	1,2,4,5,6	None	–
7	39	Female	37	1,2,3,4,6	Cushingoid appearance, hypertrichosis	–
8	61	Male	130	1,3,7	None	–
9	53	Male	23	1,3,4	None	DM, hypertension, myocardial infarction
10	46	Female	13	1,2,3,4,5,6	None	Hypertension
11	53	Female	82	1,2,3,4,5	Osteoporosis	–
12	53	Female	252	1,2,3,4	Aseptic necrosis of the femoral head	Hypertension
13	69	Female	95	1,2,3,4	Cushingoid appearance	–
14	60	Female	132	1,2,3,4,5,6,8	Cushingoid appearance, osteopenia	DM, asthma
15	42	Male	23	1,2,4,5	Cushingoid appearance	Septic arthritis
16	63	Male	47	1,3,4,5	Myopathy	Diabetes mellitus
17	50	Male	168	1,2,3,4,8	Aseptic necrosis of the femoral head	–

DM: Diabetes mellitus; 1: Systemic steroid; 2: Mycophenolate mofetil; 3: Azathioprine; 4: Intravenous immunoglobulin; 5: Plasmapheresis or Immunoadsorption; 6: Cyclophosphamide; 7: Mycophenolate sodium; 8: Methotrexate

fective than administration of prednisone alone in patients with pemphigus, and less adverse events develop (10). In the treatment guideline published in 2020, rituximab alone or in combination with steroids is recommended as the first-line treatment for mild-to-moderate/severe pemphigus. In case of rituximab contraindication, it is recommended to use a systemic steroid alone or in combination with an appropriate immunosuppressive agent (azathioprine 1–2.5 mg/kg/day or mycophenolate mofetil 2 g/day or mycophenolate sodium 1440 mg/day) (11).

There ARE two protocols: Rheumatoid arthritis protocol: 1000 mg twice a month or lymphoma protocol: 375 mg/m^2/week for a month. Treatment can be repeated 6 months after initial treatment OR in case of clinical recurrence (9). In a review of 42 studies conducted in 2012, 272 patients receiving rituximab due to pemphigus vulgaris were evaluated. 180 out of 272 patients followed lymphoma protocol, 92 followed rheumatoid arthritis protocol. It has been reported that the lymphoma protocol has a lower response and relapse rates. Rheumatoid arthritis protocol, however, has high response and relapse rates (12) in a study conducted in 2012, 42 patients were treated using the rheumatoid arthritis protocol: About 86% of the patients achieved complete remission, six patients had a complete response off therapy with an additional infusion of rituximab 6 months after initial treatment (13). In another study presenting, a 41-year-old female patient, rituximab was given using the rheumatoid arthritis protocol, but paradoxically increased lesions were observed (14). A further study treated 146 patients with the rheumatoid arthritis protocol, and although remission was achieved in an average of 6.6±3.4 months in 107 (73.3%) patients, relapse was observed in 75 (76.5%) during an average follow-up of 24.9±17.1 months (15). According to current data, there is no significant difference between these protocols in terms of duration of remission or disease-free time (7). In the present study, rituximab administration was planned in 17 patients, of whom three were not treated due to an infusion reaction and one was discharged from follow-up due to exitus. The remaining 13 patients were followed up for a median of 32 months (min: 19, and max: 99 months). During follow-up six patients had recurrences at an average 11th months and rituximab maintenance therapy (two doses of 1000 mg every 2 weeks) was applied to these patients. In one patient, relapse occurred at 7th month. At the end of the follow-up period, seven patients were in remission without any medication and five patients were in complete remission with IVIG. However, in one patient (7.6%), disease control could not be achieved after two relapses. Considering that although all patients were resistant to previous treatments and/or had contraindications to those treatments remission was achieved with rituximab in 92.3% of patients. This may suggest that rituximab is an very effective treatment in pemphigus vulgaris.

The PDAI scoring system has long been used in studies on pemphigus disease. In a prospective study using PDAI to evaluate the effectiveness of rituximab, 110 patients were followed up for 12 months after rituximab treatment, and a significant decrease in PDAI scores was observed (16). Another study used PDAI to determine the efficacy and safety of a rituximab biolike agent, in which 12 patients were followed up for 1 year and a significant decrease in scores was found (17). In the present study, the pre-rituximab values for the 13 treated patients were between 12 and 65 (mean

Table 2. Clinical responses and side effects of patients after rituximab treatment

Patient number	Concomitant medication	Time passed until control (weeks)	Complete remission time (months)	Rituximab side effects	PDAI before rituximab	PDAI last control	Latest clinical situation	Relapse number	Duration between rituximab and relapse (months)	Follow-up time after rituximab (months)
1	–	4	2	Lymphopenia	17	0	Remission with IVIG	1	6	19
2	Methylprednisolone 48 mg	4	2	–	12	0	CR	0	–	22
3	IVIG, mycophenolate mofetil	6	4	–	33	0	Remission with IVIG	1	13	61
4	IVIG	4	2	–	20	0	CR	0	–	23
5	–	4	4	–	65	0	CR	0	–	99
6	–	4	4	–	57	0	CR	0	–	89
7	Azathioprine	4	6	Lymphopenia	35	20	Relapse	2	7	62
8	–			Infusion reaction						
9	IVIG	4	2	Lymphopenia	21	0	Remission with IVIG	1	12	32
10	Methylprednisolone 8 mg, mycophenolate mofetil			Infusion reaction						
11	Methylprednisolone 32 mg, IVIG	8	4	–	29	0	CR	0	–	26
12	IVIG	8	6	–	25	0	CR	1	12	27
13	IVIG	4	2	Herpetic keratitis	15	0	CR	0	–	34
14	IVIG			Infusion reaction						
15	IVIG	6	4	Lymphopenia	20	0	CR	0	–	23
16	IVIG+100 mg methylprednisolone			Lymphopenia, cerebritis, sepsis		EX				
17	IVIG	8	13		23	0	Remission with IVIG	1	16	44

CR: Complete remission; IVIG: Intravenous immunoglobulin; PDAI: Pemphigus disease area index

28.6±15.9), while the PDAI score for 12 of these patients was zero at their last follow-up. A total of seven patients were in complete remission without medication, five patients were in remission with IVIG, and only one patient had a PDAI value of 20, suggesting that rituximab is a highly effective agent in pemphigus.

Rituximab can be used alone or in combination with systemic steroids, immunosuppressants, IVIG, plasmapheresis, or immunoadsorption (7). In the consensus panel published in 2018, although the need to combine rituximab treatment with immunosuppressive agents is uncertain, it is recommended that rituximab be combined with systemic steroids for <4 months or adjuvant immunosuppressive agents for longer than 12 months (9). In another study, it was emphasized that the combination of rituximab and IVIG is effective in resistant pemphigus vulgaris patients and does not significantly increase side effects. In the present study, rituximab was given to three patients as a monotherapy, while it was given as a combination with IVIG in six patients, with systemic steroids in one patient, with IVIG + mycophenolate mofetil in one patient, with azathioprine in one patient, and with systemic steroids + IVIG in one patient. Remission could not be achieved in the patient administered rituximab combined with only azathioprine.

Although it is accepted that rituximab is generally well tolerated and serious side effects are rare (18), in a meta-analysis including 153 pemphigus patients, the development of serious infection was reported in 11 (7.2%) patients, two of whom (1.3%) died. In another study, 4 months after rituximab treatment, one patient continued to use cyclophosphamide and prednisone, resulting in the development of severe pneumocystis carinii pneumonia (19). An analysis performed using data collected from 356 lymphoma patients treated with rituximab monotherapy reported that various (bacterial, fungal, and viral) infectious events developed in 30% of patients (20). In a further study involving 11 patients, no infection developed in those administered IVIG and rituximab in combination, although additional studies are required for verification of this trend (21). In the present study, lymphopenia developed in five patients (35.7%), four of whom recovered during follow-up, but one (7.14%) could not be followed up due to cerebritis, sepsis, and then exitus due to cranial hemorrhage. This patient who developed sepsis was receiving high-dose steroid therapy in addition to rituximab; therefore, it could not be determined whether this complication was due to steroid therapy or rituximab treatment. Moreover, herpetic keratitis was observed in one (7.14%) patient. Infusion reactions including symptoms such as hypotension, fever, chills, headache, weakness, anaphylaxis, nausea, itching, and rash can be observed with rituximab treatment (22); even Grades 3 and 4 infusion reactions can be seen in up to 10% (23); however, this situation has been shown to be prevented by premedication or slowing of the infusion (24). In the present study, despite premedication, 3 (17.6%) of the 17 patients developed a severe infusion reaction, after which the infusion was slowed but the patients' complaints continued. Finally, the infusion was stopped because the patients could not tolerate the drug.

Limitations

The low number of patients and the absence of autoantibody follow-up are considered limitations of the present study.

CONCLUSION

In the present study, considering that all patients previously received systemic steroids and at least 1 adjuvant treatment and had resistance and/or contraindications to the treatments, 92.3% achieved remission with no treatment or minimal treatment after a median follow-up of 32 months (min: 19 and max: 99 months). It can be concluded that rituximab treatment was effective in pemphigus vulgaris; however, 17.6% of patients had an infusion reaction that required discontinuation of the drug, and it is necessary to be careful in terms of side effects such as lymphopenia and infection.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 20.05.2020, number: 2020/247).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – MB, EÖS, SLÇ; Design – SLÇ, EÖS, GEG; Supervision – BM, SLÇ, DK; Resource – MB, DK, EÖS; Materials – EÖS, GEG; Data Collection and/or Processing – GEG, EÖS, SLÇ; Analysis and/or Interpretation – MB, EÖS, DK; Literature Search – EÖS, GEG, SLÇ; Writing – EÖS; Critical Reviews – MB, EÖS, SLÇ, DK, GEG.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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