Original Article

Rituximab for the Treatment of Pemphigus and Pemphigoid: A Case Series of Ten Patients

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Abstract

Background: Autoimmune bullous skin disorders are rare but potentially fatal disorders of the skin and mucous membranes. These diseases may require long-term treatment with systemic corticosteroids and other immunosuppressive drugs, which can lead to serious adverse events. Rituximab has proved to be effective form of therapy for pemphigus and pemphigoid. **Objective:** The aim of this study was to evaluate the effectiveness of a full coarse treatment with rituximab for cases of pemphigus and pemphigoid. **Materials and Methods:** A case series study involved ten cases of pemphigus and pemphigoid consulted the Dermatology Department of Merjan Teaching Hospital, Babylon, and treated with a full course of rituximab. **Results:** A complete remission (CR) has been achieved in the vast majority of cases, whereas the side effects were trivial and rare. **Conclusions:** Rituximab has proved to be effective form of therapy for pemphigus. A CR has been achieved in the vast majority of cases, whereas the side effects were trivial and rare.

Keywords: Pemphigoid, pemphigus, rituximab, treatment

Introduction

Autoimmune bullous skin disorders are rare but potentially fatal disorders of the skin and mucous membranes, and they are induced by autoantibodies against the adhesion proteins of the epidermal and dermoepidermal junction. Autoimmune bullous skin disorders are mostly characterized by a severe course, and they are potentially lethal.

These diseases may require long-term treatment with systemic corticosteroids and other immunosuppressive drugs, which can lead to serious adverse events.[1]

Pemphigus is one of the main autoimmune bullous diseases, and it is a severe blistering disease of the skin and mucous membranes. Pemphigus is mediated by pathogenic autoantibodies directed against desmoglein-1 (DSG1) and DSG3, adhesion molecules of the epidermis.

Traditionally, pemphigus cases were treated by systemic corticosteroids, often a high dose are required for prolonged periods, which expose the patients to well-documented severe side effects. Immunosuppressive agents are often used to lower the cumulative exposure to systemic corticosteroids with varying efficacy.[2]

Being an acquired autoimmune bullous disease, bullous pemphigoid (BP) is characterized by autoantibodies against a two skin basements membrane zone (BMZ) proteins, the first is type XVII collagen, a 180-kd protein, also known as BP antigen 2, and the second antigen is the 230-kd BP antigen known as BP antigen 1, which is found within the hemidesmosomes of basal keratinocytes.

Patients with BP develop tense skin blisters on inflammatory skin and often experience pruritus and urticaria-like erythematous skin lesions.

Studies have shown that more than 70% of patients with BP have elevated levels of serum IgE, while 25% of patients also have IgE deposits at the BMZ, although the predominant antibody against the BMZ components is IgG.

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Submission: 20-04-2019 **Accepted:** 16-08-2019 **Published Online:** 25-09-2019

Access this article online

Quick Response Code:

Website: www.medjbabylon.org

DOI: 10.4103/MJBL.MJBL_25_19

How to cite this article: Alwaash SS, Al-Shibly KH. Rituximab for the treatment of pemphigus and pemphigoid: A case series of ten patients. Med J Babylon 2019;16:224-8.

In standard, the therapies for BP are consisting of corticosteroids and immunosuppressants, the drugs that are known to be associated with a significant morbidity.[3]

On the other hand, mucous membrane pemphigoid (MMP) is a heterogeneous group of chronic and progressive autoimmune blistering diseases associated with tissue destruction and scarring ended with significant morbidity. Immunopathologically, MMP exhibits deposition of immune reactants at various mucosal surfaces with subsequent clinical sequelae including severe erosions, bullae, and, if allowed to progresses, fibrosis and formation of the scar tissue. Conjunctival disease can progress to blindness, and laryngeal involvement can result in airway loss.[4]

The most promising new treatment for various autoimmune diseases, including autoimmune bullous dermatoses is the monoclonal antibody rituximab.[5-8]

Rituximab is a chimeric IgG1 monoclonal antibody against CD20, a transmembrane glycoprotein, expressed exclusively on the surface of almost all B cells. Rituximab induces a transient depletion of CD201 B cells in peripheral blood within a few hours.[4-7]

The reports of rituximab treatment for pemphigus were initially begun in 2002, and these reports used the lymphoma dosage which is the only approved protocol at that time, and it continues to be used in this manner with substantial success.[9]

In 2006, rituximab was approved in the United States for rheumatoid arthritis (RA) at a different dosing schedule, of two 1000-mg infusions with a 2-week interval in adults, irrespective of body weight.

Per treatment cycle, this RA dosage offers the advantage of requiring fewer infusions and usually less medication versus the lymphoma dosage.

Pemphigus, like RA, is an autoimmune disease and does not require depletion of a malignant B-cell clone as in lymphoma. Nevertheless, the efficacy of RA dosage rituximab in pemphigus has not been established, with only five patients described in the literature to date.[10]

A Rituximab treatment has been designed in sessions, in each session rituximab was given in a dose of 375-mg/m^2 four doses weekly for 4 consecutive weeks. The first infusion is administered slowly for approximately 8 h, and subsequent infusions take 4 h.[11]

Premedication with an analgesic/antipyretic (e g, paracetamol), an antihistaminic drug (e g, chlorphenamine), and a glucocorticoids (GC) (e g, methylprednisolone) is given to reduce or avoid infusion reactions.[12]

In general, rituximab is well tolerated and serious adverse events are rare. However, infusion-related reactions include anaphylaxis, hypotension, fever, chills, headache, weakness, nausea, pruritus, and rash, which can be ameliorated by slowing the intravenous infusion rate, temporarily stopping the infusion, or beginning treatment with analgesics antihistamines, and GC.[11]

The aim of this study was to evaluate the effectiveness of a full coarse treatment with rituximab for cases of pemphigus and pemphigoid.

Materials and Methods

In this case series study, ten patients consulted the Dermatology Consultation Unit at Merjan Academic Center were recruited after verbal informed consent. Nine patients with pemphigus vulgaris (PV) and one with cicatricial pemphigoid were treated with rituximab (MabThera, Roche, Basel, Switzerland) at a dose of 375 mg/m^2 at weekly intervals for four consecutive weeks.

The diagnosis was made on the basis of clinical presentation consistent with established diagnostic criteria. Response to treatment was determined according to the definitions of an International Consensus Conference:[2] complete remission (CR) is the absence of new or established lesions and partial remission is the presence of transient new lesions that heal within 1 week. Both can be either off or on minimal therapy (≤10 mg/day of prednisone equivalent and/or minimal adjuvant therapy for at least 2 months). Relapse was defined as the appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week.

The study started with the diagnosis and treatment of the first patient at February 1, 2016 and lasted after the CR of the last case at December 1, 2017. To be included in this case series study, patients must have had a follow-up for 6 months or greater after the initiation of therapy.

All patients were presented with severe extensive generalized disease involving the mouth, while for the patient with MMP, the left eye was lost because of the disease and the right eye was initially involved with the disease. These agonies may be added to the social withdrawal and job retraction, especially for the male patients who perform a hand works in comparison to the homemaker female patients.

All patients were unresponsive to systemic immunosuppressive agent (prednisolone tablet 60 mg daily plus azathioprine 150 mg daily). Patients treated with rituximab were continued on concomitant immunosuppressive therapy, and dosing was adjusted as 5 mg prednisolone plus 50 mg azathioprine every other day.

The schedule of rituximab treatment used for our patients is the standard dose of 375 mg/m^2 body surface area (500 mg) at weekly interval for 4 weeks. Premeditations with acetaminophen and antihistamines were administered for all the patients to decrease the risk of infusion reactions. Monitoring of the patients includes complete blood count, liver function test, viral screen, and tuberculosis screen.

For the patient in whom relapse occurred, he was retreated with an additional cycle of two doses of rituximab with a

Table 1: Demographic characteristics and the study outcome of the study group (n=10)

Number	Age	Occupation	Reside	Dx	Duration of Dis. (years)	Rx	Brand	Outcome
1	20	Hand work	Diala	Cicatricial pemphigoid	2	4	Roche	Complete remission
2	40	Free work	Najaf	Pemphigus V.	2	4	Roche	Complete remission
3	60	Free work	Babil	Pemphigus V.	20	4	Roche	Complete remission
4	38	Homemaker	Babil	Pemphigus V.	9	4	Roche	Complete remission
5	42	Free work	Babil	Pemphigus V.	6	4	Roche	Complete remission
6	55	Homemaker	Babil	Pemphigus V.	8	4	Roche	Complete remission
7	47	Free work	Babil	Pemphigus V.	3	4	Roche	Partial remission
						2	Iran	Complete remission
8	35	Homemaker	Babil	Pemphigus V.	1	4	Roche	Complete remission
9	55	Employer	Babil	Pemphigus V.	6	4	Indian	Complete remission
10	50	Homemaker	Babil	Pemphigus V.	2	4	Roche	Complete remission

dose of 375 mg/m^2 at a week interval, CR has been occurred after 6 months.

Results

Demographic data of patients are presented in Table 1.

The mean duration of disease before starting immune suppression was (48.8 months). All patients had previously been unresponsive to systemic immunosuppressive regimen [Figure 1a-d]. The mean length of immunosuppression before starting rituximab was 24 months (range 12–36, standard deviation [SD] 4.48).

All the ten patients were initially treated with the lymphoma protocol for rituximab (4 weekly infusions of 375 mg/m^2). There was a mean duration of follow-up after receiving rituximab of 14 months (range 8–24, SD 3.85).

Nine patients have got CR after a rituximab cycle [Figure 2a-d] and one patient PV needed additional two rituximab infusions after 6 months of original cycle to insure CR [Table 1].

In all patients (100%) who achieved CR, the mean time from the first dose of rituximab to disease control was 13.4 months (range 6–22, SD 3.9) [Figure 3 and Table 2].

In addition to the beneficial effect in attaining CR, no side effects of rituximab treatment were noted. All patients improved socially and returned back to their jobs successfully.

During the period of follow-up, no new lesion has appeared. Oral lesions were initially improved followed by trunk lesions, and scalp lesions were the last to be healed.

For the patient with MMP, after completion of rituximab cycle, there is a dramatic improvement of the diseased eye (right) according to the opinion of the ophthalmologist.

Discussion

Pemphigus is a rare and heterogeneous group of diseases. The prolonged exposure to conventional immune-suppressing therapies can potentially increase the risks for medication-related severe adverse events.

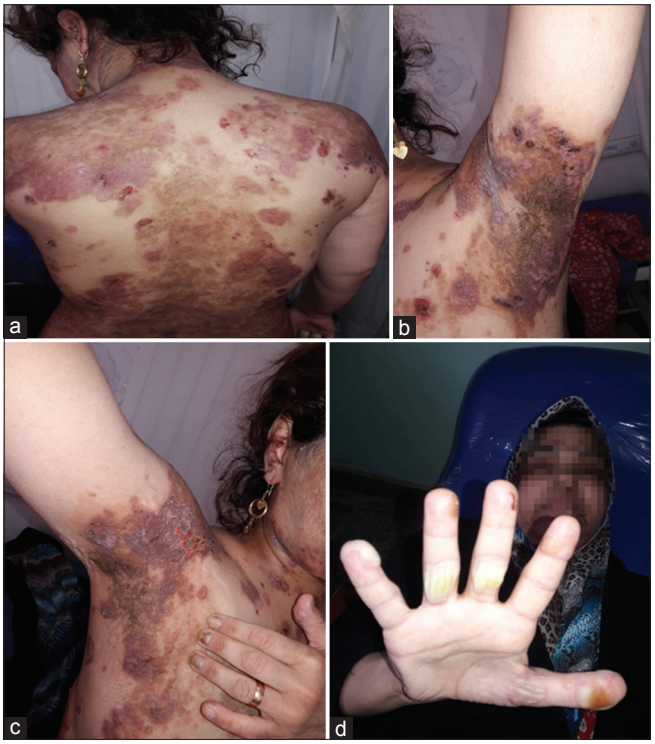

Figure 1: (a) Multiple blisters and erosions involving the back. (b) Multiple erosions and macerations involving the left axilla. (c) Multiple erosions and macerations involving the right axilla (d) Bulla and erosion involving the right hand

In our study, all patients achieved remission on treatment with rituximab. The lesions of pemphigus and MMP were healed in the whole sample of this study.

This observation is nearly consistent with data retrieved from a recent review article that summarized the available literature and found that 80%–90% of pemphigus patients showed CR on treatment with rituximab.[8]

Relapse was seen in 10% of our patients during the period of follow-up, whereas in a similar study, relapse was observed in 67% of patients, and thus, rituximab was readministered and resulted in a complete emission.[10]

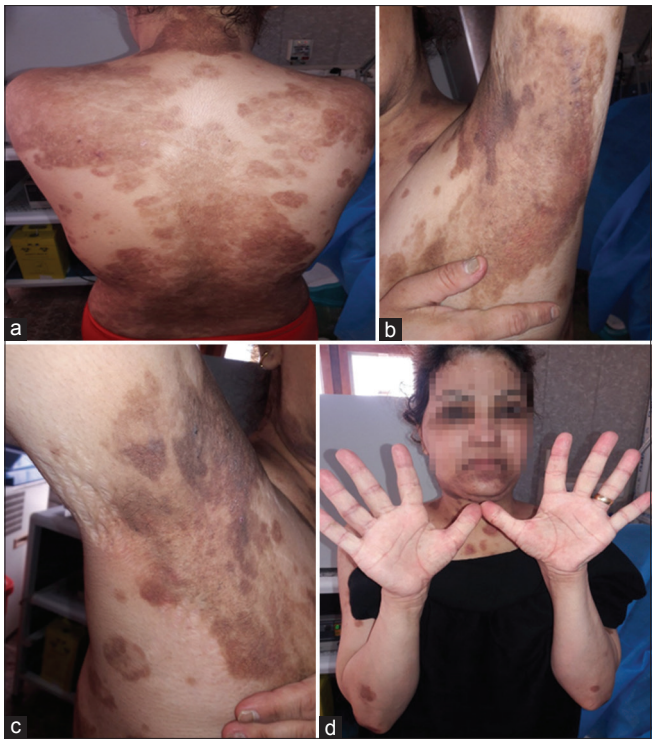

Figure 2: (a) Disappearance of blisters and erosions of the back after full course of rituximab, postinflammatory hyperpigmentation is noticed. (b) Disappearance of erosions and macerations of the left axilla after full course of rituximab, postinflammatory hyperpigmentation is noticed. (c) Disappearance of erosions and macerations of the right axilla after full course of rituximab, postinflammatory hyperpigmentation is noticed (d) Disappearance of bulla and erosion of the right hand after full course of rituximab, postinflammatory hyperpigmentation is noticed

Interestingly, previous studies have demonstrated a clinical response as early as 3–6 months after the first rituximab course.[8,9,11] However, our time to disease control was consistent with published results who had a mean time to remission of 6 months and <9–10 months which was reported by other studies as a mean time to control skin lesions after rituximab therapy.[4,7]

Many factors may influence the time needed to control the disease after rituximab treatment including the dose of the drug, the number of doses and the duration of disease before the initiation of immunosuppression.

As MMP are rare disorders, published reports are limited to case series and individual case reports, and the length of follow-up influences the reported relapse rates.

In our study, relapse was observed in 1 of 10 patients (10%) with PV after 12 months. This rate is lower compared with the 11 of 70 patients with PV (16%) treated with rituximab combined with classic immune suppressive and the two of 11 patients with PV (18%) who received rituximab and high-dose intravenous immunoglobulin as previously reported in literature.[4,5] In our relapsed patient, rituximab was readministered and resulted in CR while no adverse events were noted.[12]

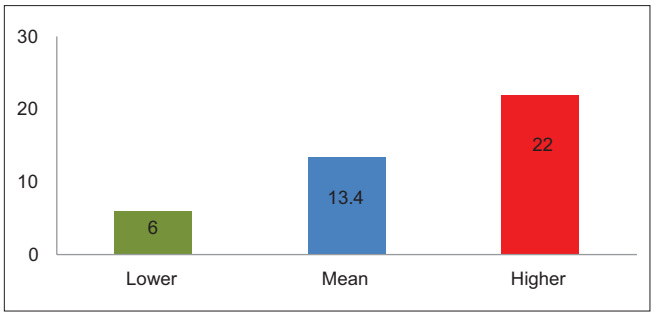

Figure 3: Time to complete remission in months after rituximab treatment, $n = 10$

Table 2: Patient information regarding the disease and its treatment

Characteristic	Patients (n=10)
Male/female	5/5
Median age at diagnosis of pemphigus (year)	46
Pemphigus vulgaris/cicatricial pemphigoid	9/1
Presence of mucosal lesions	10
Previously treated with corticosteroids	10
Previously treated with steroid-sparing treatments	10
Previous steroid-sparing treatments	10
Mycophenolate mofetil/sodium	0
Azathioprine	10
Intravenous immune globulin	0
Rituximab	0
Dapsone	0
Methotrexate	0
Cyclophosphamide	0
Median duration of disease before first dose of rituximab, month	24
Median age at time of first RA dosing of rituximab, y	48
Patients achieving disease control (complete remission)	10
Time to disease control (range) (SD), month	13 (1.87)
No. of patients off prednisone at last follow-up	0
Patients experiencing relapse after disease control	1
Time to relapse after control, month	6

SD: Standard deviation

Patients in our study were continued on systemic immunosuppression (prednisolone 5 mg tablet and azathioprine tablet 50 mg every other day) for disease control and maintenance of remission after therapy with rituximab. Use of continued immunosuppressive therapy may have increased the efficacy of therapy and delayed time to relapse which is consistent with other studies.[7-9]

In clinical trials, the most common adverse events were infusion reactions and infections, with no significant change in average immunoglobulin levels.[12]

In our study, there was no significant increase in infections with rituximab treatment compared with conventional immune suppression. Although it is also difficult to ascertain whether these side effects were attributable only to rituximab as those

patients are taking adjuvant immune suppression in addition to rituximab.

Despite the fact that deaths have been previously reported after rituximab therapy (caused by infection),[1] given the comparative efficacy, it is reasonable to conclude that superior disease control was achieved with rituximab.

Ultimately, the mean time to achieve CR in this study was 13 months which is earlier than other study that reported 18.6 months as the mean time for CR,[10] and indeed, longer than other study with mean time 6 months.

Eventually, maintenance therapy of corticosteroid and immunosuppressive agents in this case series was 5 mg prednisolone plus 50 mg azathioprine every other day, in other studies, the maintenance therapy of prednisolone was 2.5 mg daily, while adjuvant immunosuppressive were discontinued after several months.[9]

Conclusions

In this case series, rituximab has proved to be effective form of therapy for pemphigus. A CR has been achieved in the vast majority of cases, whereas the side effects were trivial and rare. Rituximab was potent in treating cases showed poor or no response with other treatment modalities such as corticosteroids and conventional immunosuppressants, such as azathioprine. These evidence in addition to the lack of long-lasting remission and the development of serious adverse effects with conventional treatment are supporting the safety and efficacy of using rituximab as the first-line treatment in patients with PV.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/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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