Received: 12 August 2023 | Revised: 21 October 2023 | Accepted: 28 October 2023

DOI: 10.1002/ccr3.8208

Clinical Case Reports Open Access WILEY

CASE REPORT

Combination therapy for management of pemphigus patients with unexpected therapeutic response to rituximab: A report of five cases

Zeinab Aryanian[1,2,3] | **Insha Zainab Riyaz**[1] | **Kamran Balighi**[1,3] | **Ali Ahmadzade**[1] | **Hamid Reza Mahmoudi**[1,3] | **Arghavan Azizpour**[1,3] | **Parvaneh Hatami**[1]

[1]Autoimmune Bullous Diseases Research Center, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

[2]Department of Dermatology, Babol University of Medical Sciences, Babol, Iran

[3]Department of Dermatology, School of Medicine Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran

Correspondence
Kamran Balighi and Parvaneh Hatami, Autoimmune Bullous Diseases Research Center, Razi hospital, vahdat-e-eslami St. Tehran University of Medical Sciences, Tehran 1199663911, Iran.
Email: kamran.balighi@yahoo.com; p_hatami2001@yahoo.com and p-hatami@alumnus.tums.ac.ir

Key Clinical Message

The immunosuppressant agents should be considered earlier in the course of treatment with rituximab, possibly after the unfavorable response at first cycle of treatment, especially in male patients and those with high BMI.

Abstract

Rituximab (RTX) has recently been proposed as an alternative first-line therapy for pemphigus patients. However, there are some rare reports of worsening of pemphigus following RTX therapy in the literature. This study aimed to evaluate the efficacy and safety of using a combination treatment of mycophenolate mofetil or dapsone and methotrexate in case of nonresponse, exacerbation or development of allergic reactions following rituximab therapy in pemphigus patients. In this case series, archive files of pemphigus patient in a tertiary care hospital from 2016 to 2021 who were treated with rituximab were reviewed and those with failure in treatment process including nonresponsiveness, exacerbation or development of allergic reactions to rituximab were identified and assessed. The study includes five patients out of 1245 RTX-treated patients, who did not respond to RTX (one patient) or experienced an exacerbation of disease (two patients) or development of allergic reactions (two patients). Male patients with high BMI (BMI > 25) whose response to rituximab was not good at first cycle and happened to receive rituximab later in the course of disease, had highest number of relapses and benefited the most from this combination immunosuppressive treatment as an alternative for repeating rituximab cycles. The lower risk of relapse and a better chance of remission might indicate the efficacy of adjuvant immunosuppressant therapy in patients with no-response, exacerbation, or allergic reaction to rituximab. These therapeutic effects were better observed in patients who received lower doses of rituximab which could suggest that the immunosuppressant agents should be considered earlier in the course of the disease, possibly after the first failed trial of rituximab therapy.

KEYWORDS
dapsone, methotrexate, mycophenolic acid, pemphigus, pemphigus worsening, rituximab

1 | INTRODUCTION

Pemphigus is a group of rare autoimmune bullous diseases that affect the skin and mucous membranes.[1] The autoantibodies (mostly in IgG form) are mainly directed against two desmosomal adhesion proteins: desmoglein (Dsg) 1 and 3, which are presented in the skin and surface-close mucosae. The binding of autoantibodies to Dsg proteins induces a separation of neighboring keratinocytes, known as acantholysis.[2]

Pemphigus is divided into three major forms: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and para-neoplastic pemphigus (PNP). Patients with PF essentially show only anti-desmoglein 1 autoantibodies and their blisters occur in the superficial layers of the epidermis.[3,4] Patients with mucosal-dominant type of PV have mostly anti-desmoglein 3 autoantibodies, whereas those with mucocutaneous type of PV have both anti-desmoglein-1,3 autoantibodies. PV blisters commonly develop deep in the epidermis or oral epithelium above the basal layer.[3,4]

Even though various treatment options are available, pemphigus is still considered a hard-to-treat disease and its treatment is still challenging. Currently, first-line therapy consists of corticosteroid administration, though additional conventional immunosuppressant agents such as mycophenolate mofetil, methotrexate, and dapsone are also used.[5–7] Rituximab (RTX) is a monoclonal antibody targeting CD20 on B lymphocytes and has recently shown a great promising effect in treating pemphigus and has even been suggested as a first-line therapy in patients with PV.[8,9] However, there are some rare reports of worsening pemphigus following RTX therapy in the literature which were mostly managed by withholding the next RTX infusions, along with other interventions such as increasing prednisolone dosage and/or IVIg administration.[10,11] However, changing the treatment protocol and using conventional immunosuppressant agents seems to be another option.

In this study we aimed to assess the characteristics of pemphigus patients who were nonresponsive to rituximab or experienced worsening of disease or allergic reaction to RTX and hence, were treated with mycophenolate mofetil, dapsone, or methotrexate.

2 | MATERIALS AND METHODS

This retrospective cross-sectional study was conducted on a group of patients of a tertiary care hospital, clinically diagnosed with pemphigus vulgaris with histopathological and immunofluorescent confirmation from January 2016 through December 2021, were enrolled in.

The study protocol was approved by the relevant ethics committee.

Patients were identified using an archiving software that contains patients' medical data, named Dermatry.ir. The following inclusion criteria were used:

All adult patients who had confirmed diagnosis of pemphigus vulgaris or pemphigus foliaceus, experienced treatment with rituximab (RTX) and were finally subjected to a combination therapy with mycophenolate mofetil, dapsone, or methotrexate due to:

- showing no improvement or deterioration after 3 months of initial rituximab treatment (nonresponsive)

or

- experiencing disease exacerbation, defined as at least a 10-point increase in Pemphigus Disease Area Index (PDAI) score within the first three-month after RTX administration [10]

or

- showing an allergic reaction after initial rituximab treatment

Patients with incomplete file records were excluded.

Demographic data, baseline comorbidities, pemphigus type, disease duration, disease severity, number of relapses, involvement sites, number of rituximab cycles and dosages, symptoms after rituximab treatment, and laboratory findings such as direct immunofluorescence (DIF), CBC, BUN, Cr, and liver enzyme profile were collected and recorded in pre-defined forms.

Nonresponsiveness to rituximab was defined as: (a) failure to enter the consolidation phase after 3 months; or (b) active disease after a maximum of 6 months; or (c) requiring >20 mg of prednisolone or equivalent after 6 months, regardless of clinical status.[12] Complete and partial remission was defined based on the 2008 Consensus statement.[13]

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics and frequencies were used to describe most of the variables and time plots were

utilized to visualize temporal variation of frequent laboratory exams.

3 | RESULTS

The study includes five patients out of 1245 RTX-treated patients, who did not respond to RTX (one patient) or experienced an exacerbation of disease (two patients) or development of allergic reactions (two patients). Allergic reactions consisted of generalized macular skin rash (in both of patients), fever (patient number 1) and arthralgia (patient number one) which were managed with an increment in prednisolone dosage. The patients' demographic data is depicted in Table 1. All five patients were male with a mean age of 42.2 and 45.6 years at diagnosis and at first visit, respectively. The average disease duration at the first visit was 45.2 months. While four patients had pemphigus vulgaris and mucocutaneous presentation, one was referred with pemphigus foliaceus diagnosis with only cutaneous involvement. The most commonly involved cutaneous sites were the face and neck, chest, abdomen, arms, genitals, and buttock and most common mucosal areas were buccal mucosa, soft palate, and anogenital site. Regarding disease severity, one patient had mild, three had moderate, and one had severe disease. In direct immunofluorescence microscopy, intra-epidermal IgG and complement C3 were observed in all patients with one patient (patient five) also having IgA deposition.

Table 2 summarizes the treatment characteristics of included patients. The number of rituximab cycles ranged from 1 to 4 and total administered doses were between 500 and 8000 mg. Before initiation of conventional immunosuppressive agents following rituximab therapy, patients one to five experienced one, five, seven, two, and one events of relapse in their disease course, respectively. When on these agents though, the relapse numbers dropped to one, three, two, two, and zero. The highest number of relapses was observed in patients who received rituximab with 8000 and 4000 mg doses. In addition, the two patients who had a time interval of more than 18 months between disease onset and first rituximab injection, demonstrated a dramatically higher number of relapses.

Overall, two of the patients received all three adjuvant drugs in their treatment course, two patient received methotrexate and either of mycophenolate mofetil or dapsone, and one patient's disease was controlled with mycophenolate mofetil alone. Methotrexate was also taken by the latter but it was immediately discontinued due to a rise in liver enzyme serum level. Initial daily dose of prednisolone was 80 mg in all but one patient. Three patients reached complete remission at the last follow up and their disease remained controlled with a daily 5 or 10 mg prednisolone.

During treatment with conventional immunosuppressants, none of the patients developed cytopenia in their lab results. Similarly, BUN and creatinine levels were mostly within normal range, with patient five having a high BUN in only one occasion. Figure 1 demonstrates the fluctuations in liver enzyme levels of each patient in respect to the type of drug received.

The immunosuppressant agents were mostly well tolerated, however, methotrexate was discontinued in one patient following an acute rise in liver enzyme levels. Unfortunately, patient three who almost always had WBC levels higher than the normal range, died at the age of 38 after developing a severe COVID-19.

4 | DISCUSSION

Recently, rituximab has been approved by FDA for the first-line treatment of pemphigus disease.[9] Some recent studies have demonstrated that early treatment with rituximab is associated with lower risk of infectious complications and adverse effects when compared to receiving rituximab after immunosuppressant agents.[14–16] By contrast, in another study, no significant difference was

TABLE 1 Patient demographics of five rituximab non-respondent cases.

Patient no.	Age[a]	Gender	BMI	Residential area	Disease type	Disease duration[b]	Disease severity	Affected areas	Comorbidities
1	55	M	42	Rural	PF	18	Moderate	S	DM, HTN, HLP
2	32	M	25	Urban	PV	48	Severe	S + M	-
3	35	M	26	Urban	PV	96	Moderate	S + M	HTN
4	58	M	25	Rural	PV	28	Mild	S + M	-
5	48	M	35	Urban	PV	36	Moderate	S + M	DM, HTN

Abbreviations: DM, diabetes mellitus; HLP, hyperlipidemia; HTN, hypertension; M, male; M, mucosal involvement; PF, pemphigus foliaceus; PV, pemphigus vulgaris; S, skin involvement.

[a]Age at first visit (years).

[b]Duration of disease at time of initiation of immunosuppressive agent (months).

TABLE 2 Treatment characteristics of five rituximab non-respondent patients.

Patient no.	RTX cycles	Total RTX dosage	Symptoms after RTX	Immunosuppressant drugs taken in the course of treatment	PRD doses at onset/3 month/6 month/ and complete remission
1	1	500 mg	A	C	80/20/15/5
2	2	4000 mg	E	M, C, D	80/20/15/10
3	4	8000 mg	N	M, D	120/25/20/no complete remission
4	2	4000 mg	E	M, C	80/20/10/5
5	2	2000 mg	A	M, C, D	80/30/12.5/no complete remissioncel

Abbreviations: A, allergic reaction; C, mycophenolate mofetil; D, dapsone; E, exacerbation; M, methotrexate; N, nonresponse; PRD, prednisolone; RTX, rituximab.

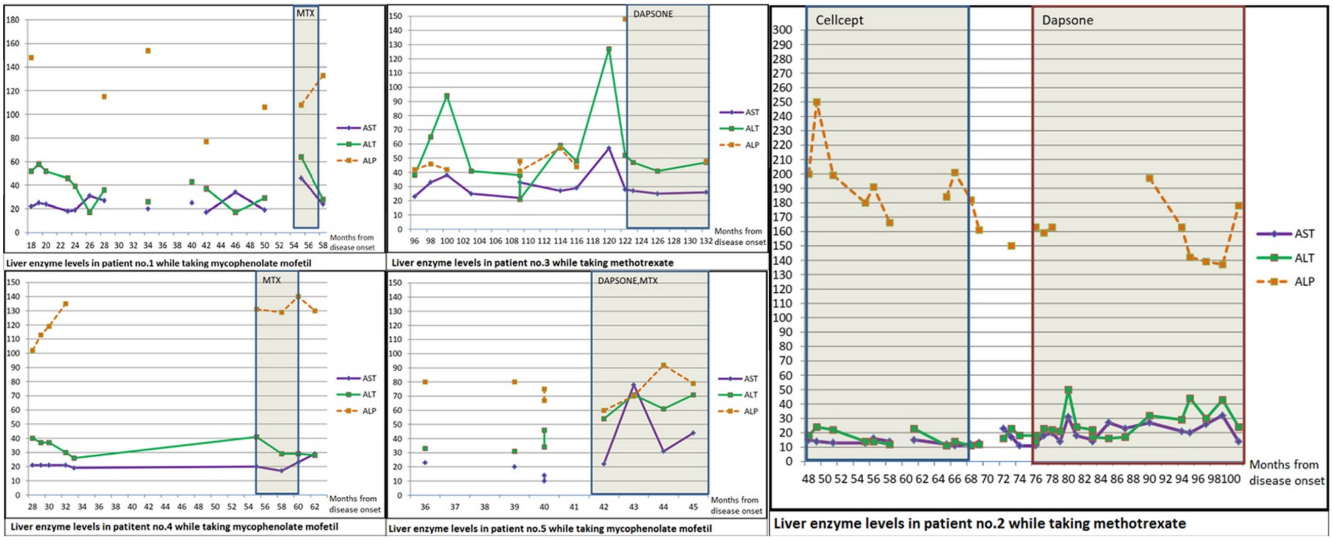

FIGURE 1 Liver enzyme levels of patients while taking conventional immunosuppressant agents. Enzyme levels are reported as international units per liter. Highlighted portions show the duration when corresponding drugs were also received by the patients.

observed between early and later rituximab treatment in regards to its safety; However, a higher chance of complete remission and a longer disease remission was observed in the early treated patients.[17] Overall, rituximab adjuvant therapy has been associated with a remission rate of 76% to 89%.[9,18–20] However, paradoxical exacerbation of disease was reported at 1.12% and 0.38% per patient and cycle, respectively.[11] Though there is no exact explanation for this phenomenon, some speculations could be hypothesized including the incomplete depletion of autoreactive clonal B cells after treatment with rituximab, involvement of some specific anti-Dsg3 T cells, depletion of regulatory $CD20^+$ B cells which might lead to an imbalance in proportion of B cell population towards more number of effector B cells, development of inhibitory antibodies to the RTX or some genetic polymorphisms.[10,11]

In patients with a moderate to severe disease who are nonrespondent to rituximab, the current guidelines recommend increasing the adjunct prednisolone dose or administering intravenous corticosteroid pulses.[21] Other recommended treatments for patients with severe or refractory disease include: intravenous immunoglobulins (IVIG) administration and immune adsorption.[21] The exact role of conventional immunosuppressive agents, in resistant patients who receive rituximab as first-line treatment remains unclear.

In this study, the characteristics of five pemphigus patients with failure to treatment with rituximab were discussed. All of the included patients were male, and were labeled as overweight or obese based on their BMI scores. It can be suggestive that overweight male patients are more prone to be inappropriate cases for treatment with RTX.

An interval of less than a month between disease onset and start of RTX was associated with a lower number of relapses in our patients, with the highest number of relapse observed in those with intervals greater than 18 months. In addition, rituximab doses of 4000 and 8000 mg had a higher number of relapses compared to those who received fewer amounts. This could suggest that the dose of rituximab and the time interval between the onset of disease and start of rituximab treatment are important factors in predicting the future relapses. Previously, an Iranian guideline for rituximab therapy in pemphigus has also suggested earlier use of rituximab in the course of disease.[22]

Overall, the number of relapses decreased for patients while being treated with mycophenolate mofetil, methotrexate or dapsone and subsequently, at the last follow up, three patients had reached complete remission. The lower risk of relapse and the better chance of remission might indicate the efficacy of adjuvant immunosuppressant therapy in patients with failure to treating with rituximab. These therapeutic effects were better observed in patients who received lower doses of rituximab which could suggest that the dose of rituximab and the time interval between the onset of the disease and the start of rituximab treatment are important factors in predicting future relapses. Hence, the immunosuppressant agents should be considered earlier in the course of treatment, possibly after the first failed trial of rituximab therapy.

In summary, results of this small case series demonstrated the therapeutic potential of conventional immunosuppressant agents for the management of pemphigus patients with nonresponsiveness or contraindications to rituximab. This was of a greater importance in the COVID era which using the higher doses of corticosteroids in pemphigus patients was a concerning controversial issue. Still, larger and more robust studies are needed to further investigate the efficacy of these immunosuppressive drugs and to determine the optimal treatment timing for them.

AUTHOR CONTRIBUTIONS

Zeinab Aryanian: Investigation; supervision. **Insha Zainab Riyaz:** Data curation; formal analysis. **Kamran Balighi:** Conceptualization; formal analysis. **Ali Ahmadzade:** Methodology; writing – original draft. **Hamid Reza Mahmoudi:** Investigation; project administration. **Arghavan Azizpour:** Validation; visualization. **Parvaneh Hatami:** Data curation; writing – review and editing.

ACKNOWLEDGMENTS

The authors would like to thank Razi Hospital Clinical Research Development Center and Autoimmune Bullous Diseases Research Center for their technical and editorial assistance.

FUNDING INFORMATION

We received no funding for this project.

CONFLICT OF INTEREST STATEMENT

All the authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patients to publish this report in accordance with the journal's patient consent policy.

ORCID

Arghavan Azizpour https://orcid.org/0000-0003-2187-5466
Parvaneh Hatami https://orcid.org/0000-0002-3531-2907

REFERENCES

1. Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. *Immunol Res*. 2018;66(2):255-270.
2. Schmidt E, Kasperkiewicz M, Joly P. Pemphigus. *Lancet*. 2019;394(10201):882-894.
3. Kasperkiewicz M, Ellebrecht CT, Takahashi H, et al. Pemphigus. *Nat Rev Dis Primers*. 2017;3(1):1-18.
4. Baican A, Chiorean R, Leucuta DC, et al. Prediction of survival for patients with pemphigus vulgaris and pemphigus foliaceus: a retrospective cohort study. *Orphanet J Rare Dis*. 2015;10(1):1-14.
5. Martin LK, Agero AL, Werth V, Villanueva E, Segall J, Murrell DF. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev*. 2009 Jan 21; (1).
6. Harman K, Brown D, Exton L, et al. British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017. *Br J Dermatol*. 2017;177(5):1170-1201.
7. Carson PJ, Hameed A, Ahmed AR. Influence of treatment on the clinical course of pemphigus vulgaris. *J Am Acad Dermatol*. 1996;34(4):645-652.
8. Balighi K, Hatami P, Sheikh Aboli MJ, et al. Multiple cycles of rituximab therapy for pemphigus: a group of patients with difficult- to-treat disease or a consequence of late rituximab initiation? *Dermatol Ther*. 2021;8:e15249. doi:10.1111/dth.15249
9. Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. *Lancet*. 2017;389(10083):2031-2040.
10. Mahmoudi H, Balighi K, Tavakolpour S, Daneshpazhooh M. Unexpected worsening of pemphigus vulgaris after rituximab: a report of three cases. *Int Immunopharmacol*. 2019;71:40-42. doi:10.1016/j.intimp.2019.02.037
11. Nili A, Tavakolpour S, Mahmoudi H, Noormohammadpour P, Balighi K, Daneshpazhooh M. Paradoxical reaction to rituximab in patients with pemphigus: a report of 10 cases. *Immunopharmacol Immunotoxicol*. 2020;42(1):56-58. doi:10.1080/08923973.2020.1717526
12. Shakshouk H, Daneshpazhooh M, Murrell DF, Lehman JS. Treatment considerations for patients with pemphigus during the COVID-19 pandemic. *J Am Acad Dermatol*. 2020;82(6):e235-e236.
13. Mahmoudi H, Tavakolpour S, Balighi K, Farid AS, Nili A, et al. Rituximab in practice: clinical evaluation of patients with pemphigus after rituximab administration. *Dermatol Ther*. 2021;34(1):e14633.

14. Murrell DF, Dick S, Ahmed A, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol*. 2008;58(6):1043-1046.
15. Boulard C, Duvert Lehembre S, Picard-Dahan C, et al. Calculation of cut-off values based on the autoimmune bullous skin disorder intensity score (ABSIS) and pemphigus disease area index (PDAI) pemphigus scoring systems for defining moderate, significant and extensive types of pemphigus. *Br J Dermatol*. 2016;175(1):142-149.
16. Aryanian Z, Balighi K, Daneshpazhooh M, et al. Rituximab exhibits a better safety profile when used as a first line of treatment for pemphigus vulgaris: a retrospective study. *Int Immunopharmacol*. 2021;96:107755.
17. Balighi K, Daneshpazhooh M, Mahmoudi H, et al. Comparing early and late treatments with rituximab in pemphigus vulgaris: which one is better? *Arch Dermatol Res*. 2019;311(1):63-69.
18. Bozca BC, Bilgiç A, Uzun S. Long-term experience with rituximab therapy for treatment-resistant moderate-to-severe pemphigus. *J Dermatolog Treat*. 2021;1-8:2102-2109.
19. Wang H-H, Liu C-W, Li Y-C, Huang Y-C. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Derm Venereol*. 2015;95(8):928-932.
20. Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. *Autoimmun Rev*. 2015;14(4):323-331.
21. Joly P, Horvath B, Patsatsi A, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). *J Eur Acad Dermatol Venereol*. 2020;34(9):1900-1913.
22. Daneshpazhooh M, Balighi K, Mahmoudi H, et al. Iranian guideline for rituximab therapy in pemphigus patients. *Dermatol Ther*. 2019;32(5):e13016.

How to cite this article: Aryanian Z, Riyaz IZ, Balighi K, et al. Combination therapy for management of pemphigus patients with unexpected therapeutic response to rituximab: A report of five cases. *Clin Case Rep*. 2023;11:e8208. doi:10.1002/ccr3.8208