

# Treatment of severe pemphigus vulgaris with rituximab

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**Abstract** Pemphigus vulgaris is an autoimmune skin disease mediated by autoantibodies directed against desmoglein-3 and desmoglein-1 located on keratinocytes. Rituximab, a monoclonal anti-CD20 antibody depleting B-cells, offers an effective treatment possibility for therapy-resistant pemphigus vulgaris. Here, we present a case of 20-year-old female who did not respond sufficiently to conventional treatment with prednisolone, azathioprine, mycophenolate mofetil and intravenous immunoglobulins but underwent almost complete remission after rituximab treatment. It was given as two injections of 500mg each at an interval of two weeks in ICU setting.

**Key words**

Pemphigus vulgaris (PV), Desmoglein.

## Introduction

Pemphigus vulgaris is a severe life threatening autoimmune blistering disorder characterized by flaccid blisters and painful erosions involving the skin and mucosa.<sup>1</sup> It is caused by autoantibodies against the cell surface adhesion proteins on keratinocytes, the desmogleins. Desmoglein-1 (Dsg-1) is primarily expressed in the upper level of epidermis and weakly in the squamous mucosae, whereas Desmoglein-3 (Dsg-3) is expressed strongly in mucosa and weakly in the epidermis. Autoantibodies in PV are predominantly directed against Dsg-3. The binding of autoantibodies results in loss of cell-cell adhesion and blister formation.<sup>2</sup>

Systemic corticosteroids in combination with immunosuppressive agents, used to decrease the production of autoantibodies, are the mainstay of treatment for pemphigus vulgaris. Their long

term use is associated with adverse effects and complications which contribute to morbidity and mortality of the disease. Alternative treatments options used for these patients are pulse administration of high-dose steroids or cyclophosphamide, plasmapheresis, photopheresis, intravenous immunoglobulins, mycophenolate mofetil and immunoabsorption.<sup>3</sup>

Rituximab is a chimeric murine-human anti-CD20 monoclonal antibody directed against CD20 positive B cells.<sup>2</sup> Rituximab causes death of CD20 positive cells by complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity thus leading to a decline of circulating anti-desmoglein autoantibodies<sup>4</sup>. Therefore, rituximab has been reported to be beneficial in treating PV. It is administered either by Lymphoma protocol or Rheumatoid Arthritis protocol.<sup>4</sup>

## Case report

A 20 years old unmarried female having history of severe pemphigus vulgaris for two years presented with multiple large erosions with hemorrhagic crusting on face, neck, front of

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**Figure 1** Before rituximab: Erosions, hemorrhagic crusting and bleeding on breast



**Figure 2** Before rituximab: Erosions with crusting on face



**Figure 3** After rituximab (15 days after second cycle): Healing with postinflammatory hyperpigmentation on breast



**Figure 4** After rituximab (15 days after second cycle): Healing with postinflammatory hyperpigmentation on face.

chest, abdomen, back of trunk, axillae, groins and buttocks. There were multiple painful erosions involving buccal mucosa, tongue and hard palate. No other mucosa was involved. She had previous two admissions with the same condition in Tertiary care hospital. Histopathology showed supra-basal cleft with tombstoning. Immunofluorescence could not be done. She was given high dose steroids (70mg of prednisolone), azathioprine, mycophenolate mofetil and intravenous immunoglobulins. She had developed steroid induced hypertension, diabetes and cushingoid features. As the patient responded partially and developed severe side effects of steroids, Rituximab infusion was planned.

After taking informed consent from the patient, workup for Rituximab was done which included T-spot test for tuberculosis, HRCT, PCR for Hepatitis B and C, ESR, blood biochemistry and ECG.

Rituximab was infused in ICU as per Rheumatoid Arthritis protocol (1000 mg twice, 2 weeks apart). Pre-medication with Inj Solucortef 500mg IV, 2 tablets Panadol 500mg, Inj Avil 2ml was given 30 mins before infusion. First infusion (500mg/50ml vial in 200ml Normal Saline) was administered at a rate of 50mg/hr IV, escalated every 30min by 50mg/hr to a maximum infusion rate of 300mg/hr. Second vial (500mg) infusion was given at last

maintenance dose rate (300mg/hr). Total infusion time was 5 hours. Cardiac monitoring was done and vitals were checked every 15 minutes. Patient was monitored for any anaphylactic reactions and side effects during and after infusion. Second cycle of Rituximab was given after 2 weeks interval.

After the first cycle of rituximab, patient still developed new blisters for 5 days and had crusted erosions. No new blister formed from 6<sup>th</sup> day onwards after first cycle of rituximab and patient's previous erosions started to heal. Oral erosions also showed improvement. After the second cycle of rituximab, marked improvement was seen in all the erosions. Most of the lesions healed in 15 days leaving post inflammatory hyperpigmentation. No adverse effects of rituximab were documented. Azathioprine 150 mg and prednisolone 30mg were continued with rituximab treatment.

## Discussion

Treatment of pemphigus vulgaris is prolonged with oral corticosteroids and immune-suppressants having serious side effects. Some cases even do not respond.<sup>5</sup>

Rituximab is a chimeric monoclonal antibody against CD20 + B-cell surface antigen. It acts against autoreactive and mature B cells and against Dsg-3 specific autoreactive T cells and spares plasma cells. It has been approved since 1997 by the US Food and Drug Administration for the treatment of CD20 + B-cell lymphoma, non-Hodgkin lymphoma, and rheumatoid arthritis.<sup>6</sup> Rituximab has been successfully administered in patients with treatment-resistant autoimmune bullous diseases such as paraneoplastic pemphigus, pemphigus vulgaris and pemphigus foliaceus.<sup>7</sup>

Treatment guidelines recommended rituximab as second or third line treatment option for pemphigus.<sup>8</sup> However, a study done by Joly *et al.*<sup>9</sup> used rituximab with low dose corticosteroids as first line of treatment. 85% of patients achieving clinical remission during 36 months follow up<sup>9</sup>. Recent recommendations suggest the use of rituximab as first line treatment option for moderate to severe pemphigus.<sup>10</sup>

In the treatment of pemphigus vulgaris, no standard protocol for rituximab dosage is present. In most cases, rituximab is administered either by Lymphoma protocol (375 mg/m<sup>2</sup> once a week for 4 weeks) or Rheumatoid Arthritis protocol (two doses of 1,000 mg 2 weeks apart).<sup>4</sup> In a review, Ahmed and Shetty reported similar response rates in pemphigus vulgaris for both protocols.<sup>11</sup>

In a study of 103 pemphigus vulgaris patients treated with rituximab, Schmidt *et al.* reported complete remission in 77% and partial remission in 21% of the patients.<sup>12</sup>

Adverse effects of rituximab includes: infusion-related side-effects, such as headache, fever, chills, urticaria, pruritus and hypotension which are usually mild and can be controlled or prevented by premedication with paracetamol (acetaminophen) and antihistamines. Cardiovascular complications like sinus tachycardia, dysrhythmia and myocardial ischemia can occur.<sup>4</sup> However, both life-threatening and fatal opportunistic infections have been reported following rituximab therapy particularly when combined with immunosuppressants.<sup>7</sup>

In our patient, two cycles of rituximab therapy together with conventional immunosuppressive treatment resulted in remarkable clinical improvement. No side effect of rituximab was seen in our patient.

However, more studies should be done on more number of patients to see efficacy and long term safety of rituximab in pemphigus vulgaris.

## Conclusion

Rituximab appears to be a promising new treatment modality for pemphigus vulgaris because of its high efficacy in treating resistant cases and its minimal short-term side effects.

## References

1. Büsing V, Kern J, S, Bruckner-Tuderman L, Hofmann S, C: Recalcitrant Pemphigus Vulgaris Responding to Systemic Tacrolimus. *Dermatology*. 2010;**221**:122-6. doi: 10.1159/000314155
2. Ioannides D, Lazaridou E, Rigopoulos D. Pemphigus. *J Eur Acad Dermatol Venereol*. 2008;**22(12)**:1478-96. doi: 10.1111/j.1468-3083.2008.02825.x. PMID: 18637862.
3. Mutasim DF. Management of autoimmune bullous diseases: pharmacology and therapeutics. *J Am Acad Dermatol*. 2004;**51(6)**:859-77; 878-80. doi: 10.1016/j.jaad.2004.02.013. PMID: 15583576.
4. Kanwar AJ, Vinay K. Rituximab in pemphigus. *Indian J Dermatol Venereol Leprol*. 2012;**78(6)**:671-6. doi: 10.4103/0378-6323.102354. PMID: 23075635.
5. Gregoriou S, Efthymiou O, Stefanaki C, Rigopoulos D. Management of pemphigus vulgaris: challenges and solutions. *Clin Cosmet Investig Dermatol*. 2015;**8(1)**:521-7.
6. Storz U. Rituximab: how approval history is reflected by a corresponding patent filing strategy. *MAbs*. 2014;**6(4)**:820-37. doi:10.4161/mabs.29105.
7. Schmidt, E., Hunzelmann, N., Zillikens, D., Brocker, E.-B., & Goebeler, M. Rituximab in refractory autoimmune bullous diseases. *Clin Exp Dermatol*. 2006;**31(4)**:503-8. <https://doi.org/10.1111/j.1365-2230.2006.02151>.
8. Hertl M, Jedlickova H, Karpati S, et al. Pemphigus. S2 Guideline for diagnosis and treatment--guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol*. 2015;**29(3)**:405-14. doi:10.1111/jdv.12772.
9. Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux3): A prospective, multicentre, parallel-group, open-label randomised trial. *Lancet Lond Engl* 2017;**389**:2031-40.
10. Murrell DF, Peña S, Joly P, Marinovic B, Hashimoto T, Diaz LA, et al. Diagnosis and management of pemphigus: Recommendations by an international panel of experts. *J Am Acad Dermatol*. 2018. pii: S0190-9622(18)30207-X. doi: 10.1016/j.jaad.2018.02.021.
11. Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. *Autoimmun Rev*. 2015;**14**:323-31. 10.1016/j.autrev.2014.12.002.
12. Schmidt E, Goebeler M, Zillikens D. Rituximab in severe pemphigus. *Ann N Y Acad Sci*. 2009;**1173**:683-91.