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**Case Report**

# Rituximab as first line: an advent in pemphigus

**V. P. K. Gopinath, Basheer Ahammed Kolaparambath, V. M. Simi, C. M. Ali Rishad*, P. M. Farisa, Tresy Jose**

Department of Dermatology, MES Medical College, Malappuram, Kerala, India

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***Correspondence:**
Dr. C. M. Ali Rishad,
E-mail: dralirishadcm@gmail.com



## ABSTRACT

Rituximab is a newly approved biological wonder drug in pemphigus vulgaris- an autoimmune mucocutaneous blistering disease due to antibodies produced against the epidermal adhesion molecules dsg 1 and dsg 2. The conventional therapy included high dose steroids or immunosuppressants that though effective had significant adverse effects that necessitated an alternate path in treatment. We present a case series of five patients in different clinical scenarios diagnosed with pemphigus vulgaris and treated with Rituximab by RA protocol either sole or in combination with other treatment strategies. Our experience with this drug has paved way to immense possibilities and outcomes that are in favour of using Rituximab as first line option. We have encountered prolonged remission in cases that were treated with Rituximab by Rheumatoid arthritis (RA) protocol. The sustained response has helped in reducing the dose of steroids and other immunosuppressants substantially. These facts are reinforced through our observations. But there is need to standardize the dosage of Rituximab in pemphigus.

**Keywords:** Pemphigus vulgaris, Rituximab, HACA, Plasmapheresis

## INTRODUCTION

Pemphigus vulgaris (PV) is a chronic autoimmune blistering disease affecting both the skin and mucous membranes characterized by presence of circulating auto antibodies formed against epidermal adhesion molecules like dsg 1 and dsg2 resulting in intra-epidermal blister formation.[1] Until recently, steroids were the mainstay of therapy. Although effective, the side effects necessitated an alternative. Pulse therapy with immunosuppressants, antimetabolites, intravenous immunoglobulins and biologicals like Rituximab are some of the other therapeutic options introduced in recent years.

Rituximab, a chimeric monoclonal antibody against the protein CD20 positive B-cell specific antigen produces a targeted immunosuppresion so that adverse effects are comparatively less.[2] Though FDA has approved the drug for use in pemphigus vulgaris, due lack of specific guidelines we either follow RA protocol, lymphoma protocol or low dose protocol

Rituximab is a novel drug for PV, especially when response to conventional therapy fails.[3] However, the expense of formulation has made it unaffordable to the vast majority of Indian patients.

This is a case series of 5 patients of PV treated with Rituximab.

## CASE REPORTS

### *Case I*

38/M with erosions all over body and buccal mucosa (Figure 1 a and b). Skin biopsy, DIF (direct

immunofluorescence) consistent with PV. Started on DCP (dexamethasone cyclophosphamide pulse)- 3 pulses, no response (Figure 1 c and d). In between he developed complications of hypoproteinemia, hyponatremia and recurrent bacterial infections. Thence he was treated with Rituximab as per RA protocol (Figure 1 e and f). He achieved remission within 2 weeks and continues so for last 1½ years.

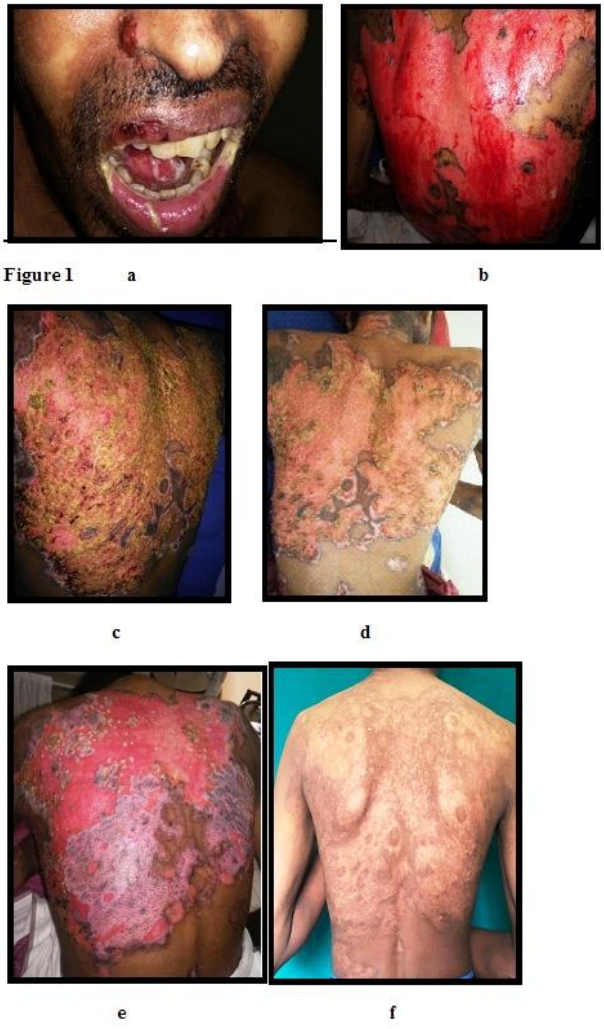


**Figure 1: Case I- no response to DCP; remission with Rituximab.**

***Case II***

23/M presented with erosions over entire body and buccal mucosa (Figure 2 a and b). Skin biopsy, DIF consistent with PV. Started on steroid pulse followed by DCP. In between he developed cushingoid features (Figure 2c) as an adverse effect. In addition to this he relapsed (Figure 2d) after 3 pulses. So, we initiated Rituximab as per RA protocol. Remission achieved (Figure 2 e and f) within 2 weeks of infusion. He is free of steroids for last 1 year.


**Figure 2: Case II- relapsed with DCP; remission with Rituximab**

***Case III***

41/M, a known case of pemphigus vulgaris treated from outside with Rituximab as per lymphoma protocol but relapsed after 6 months and presented to us with erosions over entire body (Figure 3a). Patient treated with 2 cycles of plasmapheresis followed by low dose Rituximab (500 mg 2 weeks apart) and in remission (Figure 3 b and c) for a year.

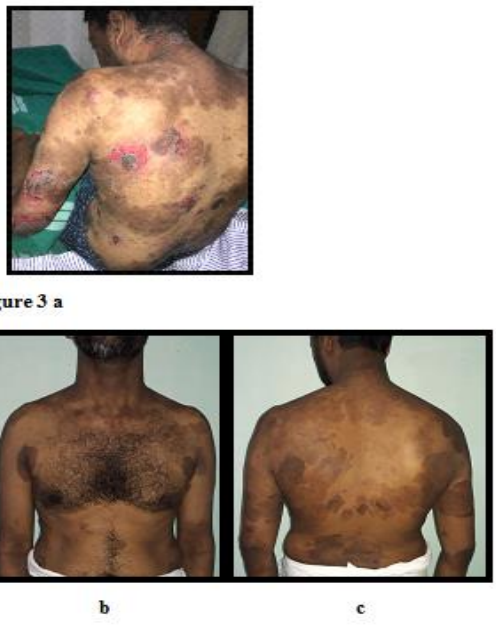


**Figure 3: Case III- remission with combined therapy of Rituximab and plasmapheresis.**

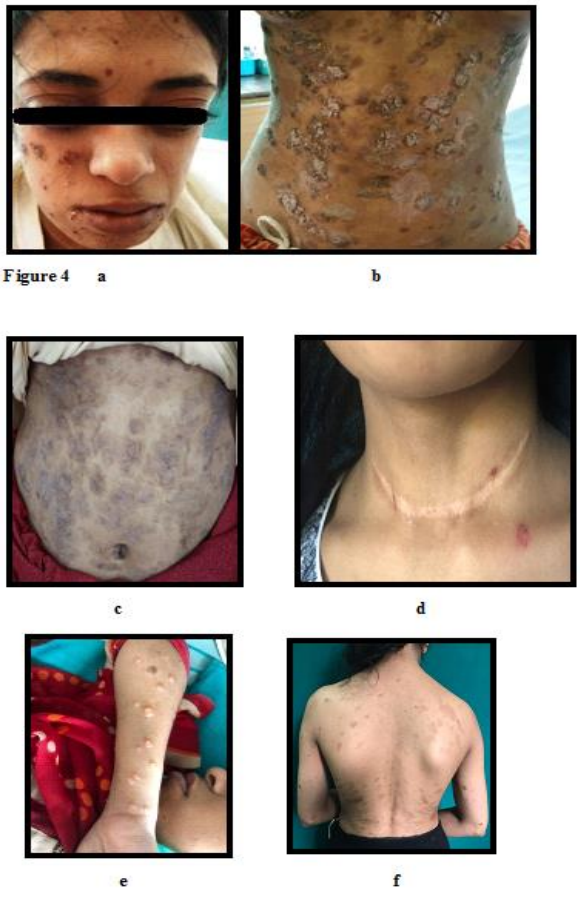


**Figure 4: Case IV- temporary remission achieved with Rituximab and relapsed after 6 months. Remission with oral steroids.**

***Case IV***

17/F a known case of Graves` disease presented with fluid filled lesions over the body including buccal mucosa (Figure 4 a and b). Skin biopsy, DIF consistent with PV. Considering her financial constraints and dramatic outcome of previous cases we started treating with low dose Rituximab. She achieved remission within 2 weeks of infusion (Figure 4c). She had hypotension during each infusion which was managed appropriately by reducing the rate of infusion. Unfortunately, she relapsed after 6 months (Figure 4d). We gave additional 2 doses of 500 mg of Rituximab. She had multiple new lesions in spite of this (Figure 4e). So we administered oral steroids additionally. Now she is under remission with oral steroids only (Figure 4f).


**Figure 5: Case V- disseminated varicella infection in remission period with Rituximab.**

***Case V***

77/F with recurrent oral ulcers and multiple vesicles over entire body. Skin biopsy and DIF consistent with PV (Figure 5a). She was initially treated with oral steroids but failed to respond adequately so we put her on low dose Rituximab. After first dose itself she responded well with healing of lesions. But she developed varicella infection (Figure 5 b and c) after the first dose and was unresponsive to treatment with intravenous Acyclovir leading to viral encephalitis and subsequently expired.

## DISCUSSION

Dr. Neil Shear said "*Rituximab* acts *like putting water on fire* in pemphigus.[4]

We administered Rituximab in five different clinical scenarios of patients diagnosed with pemphigus vulgaris. First case did not respond to DCP, second one relapsed with DCP, third case relapsed after Rituximab, fourth case had an underlying auto immune disorder and fifth case developed disseminated varicella infection as complication of treatment. All patients irrespective of dose responded initially. Except hypotension in one patient no other side effects issued during infusion. Hypotension was managed by lowering the rate of infusion. Another patient on low dose relapsed after 6 months and needed 2 additional doses of Rituximab and oral steroids. One patient expired due to viral encephalitis.

Pemphigus vulgaris is a blistering disease affecting the desmoglein protein 1 and 2 that results in intra-epidermal supra-basal blisters in the skin and mucous membrane. Amongst the different treatment options available the most widely accepted mainstay of therapy remains high dose steroids. Unfortunately there are significant side effects noted in relation to them.[5] Other therapies include immunosuppressants, Intravenous immunoglobulins and Rituximab, a biological drug.

Rituximab, genetically engineered chimeric murine/ human monoclonal IgG1 kappa antibody directed against the CD20positive B-cell specific antigen produces a targeted immune suppresion so that adverse effects are comparatively less. Rituximab is effective in treating moderate to severe pemphigus vulgaris especially when conventional treatment fails.[6] It not only helps to minimise the duration of steroids and other immunosuppressants by inducing fast and prolonged remission but also decreases the need to administer them to nil and hence considered in the adjuvant therapy. More effectual when delivered in the beginning of the disease process.[7] The drug is now FDA approved for use in pemphigus on the basis of many studies depicting its significant efficacy outweighing risks, particularly by the study carried out by Joly et al in France.[8]

The most commonly followed regimen is the lymphoma protocol.[9] Here we have followed the Rheumatoid arthritis protocol. Some studies recommend use of rituximab by the RA protocol citing lesser relapse rates and longer remission periods. There is an urgent need to standardize the dosage specific to pemphigus so as to compare varied studies in efficacy.

When compared to conventional therapy, a combination of the drug with plasmapheresis shows a reduction in circulating autoantibodies.[10] It thus becomes an useful alternative in patients with contraindications to conventional therapy.

In those with other associated autoimmune disorders relapse is commonly seen.[11,12] Relapse may be attributed to this development of Human anti-chimeric antibodies (HACA) that is primarily caused by incomplete B cell depletion.[13] Low doses of the drug may be implicated as the underlying cause of incomplete B cell depletion. There are no kits available for measurement of HACA. Development of HACA is more common in autoimmune diseases than in lymphoma.[14] Therefore in net effect low doses of Rituximab is inadequate in treating autoimmune diseases. But when combined with plasmapheresis, circulating antibodies are reduced that justifies lower dosages of the drug.[15]

It is quite an added bonus here that Rituximab induces a positive effect in interrupting the disease course of Thyroid associated ophthalmopathy and is considered as a possible therapeutic option.[16]

There is no particular patient selection criteria specified in literature and age plays no role in prognosis but a study by Payet et al has results otherwise.[17,18]

Infusion reactions when they occur can be within 1-2 hours of the first infusion (30-35%).[19] These maybe in the form of fever, headache, rigors, flushing, nausea, rash, URTI symptoms etc. Transient hypotension and bronchospasm are usually related to the infusion rate and hence considerably managed by reducing the rate.[20]

Many infections are often encountered in the post infusion period. Disseminated varicella infection, HSV, HZV, progressive multifocal leukoencephalopathy by JC virus being some among them. This warrants the need for prophylactic vaccinations in those preventable.[21] The drug is classified under schedule C.

Though Rituximab has a high upfront cost but the overall expense in terms of hospital visits and stays, in the duration of the disease, is better as compared to other pulse therapies(; thereby reducing the burden of disease.[22]

## CONCLUSION

Rituximab, the recently approved FDA drug in pemphigus, is a potent agent yielding fast and sustained remission that can actually be considered as first line drug in the disease. Age is one factor that is to be taken into account during patient selection process. Low doses though effective, relapse rates are more encountered. HACA, one cause of relapse has been observed more in females and those with associated autoimmune diseases. A combination of the drug with plasmapheresis can significantly cause an impact by producing sustained remission and then justifies lower doses. Infections especially varicella are seen in the post infusion period which may be prevented by prophylactic vaccinations.

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