



Resident's Page

Rituximab in pemphigus vulgaris - Standard operating procedure

Kidangazhiathmana Ajithkumar¹, Sneha Johny¹, Pinky Salim¹, Neelakandhan Asokan¹

¹Department of Dermatology and Venereology, Government Medical College, Thrissur, Kerala, India.

***Corresponding author:**

Kidangazhiathmana
Ajithkumar,
Department of Dermatology
and Venereology, Government
Medical College, Thrissur,
Kerala, India.

ajisudha@gmail.com

Received : 31 December 2020

Accepted : 22 March 2021

Published : 14 October 2022

DOI

10.25259/JSSTD_66_2020

Quick Response Code:



ABSTRACT

Treatment of pemphigus poses a significant challenge in dermatology practice. Rituximab has recently been accepted as a first-line drug for pemphigus. This article tries to propose a standard operating procedure for the administration of rituximab.

Keywords: Pemphigus, Rituximab, Standard operating procedure

INTRODUCTION

Treatment of pemphigus group of disorders is a major challenge in dermatology practice. Rituximab is a recent addition in the armamentarium against this disease and has recently been accepted as a first-line treatment.^[1-3] It is a 145 kDa chimeric murine - human monoclonal antibody directed against CD20 antigen expressed on B-cells.^[4] FDA (food and drug administration) approved rituximab for the treatment of adults with moderate-to-severe pemphigus vulgaris in 2018.^[5]

This article tries to propose a standard operating procedure for the administration of rituximab.

All patients diagnosed with pemphigus may be given the option of rituximab.

Before opting for rituximab, patients should be educated regarding the possible benefits, expected outcome of treatment, and the probable adverse events.

Advantages

- Rituximab at spaced intervals can sufficiently control the disease activity in pemphigus and can substitute the prolonged and daily treatment with other immunosuppressants^[1,6]
- Following an initial period of combination treatment with systemic steroids, rituximab permits a faster tapering and withdrawal of the former. This in turn helps to avoid the side effects of long-term treatment with corticosteroids^[1]
- Rituximab may help to avoid other steroid-sparing agents that may be required daily on a long-term basis^[2]
- As per the existing evidence, there is an 80% chance of achieving drug-free remission in 2 years.^[1]

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

©2022 Published by Scientific Scholar on behalf of Journal of Skin and Sexually Transmitted Diseases

Disadvantages

- Possibility of severe immunosuppression and infections^[7-10]
- High cost compared to corticosteroids and most of the other steroid-sparing drugs
- The need for immunization against various infectious agents^[10]
- Pre-treatment evaluation requiring expensive investigations
- A comparatively limited period of experience with the drug.

Rituximab can be the therapeutic option in the following scenarios:

- Those who failed to respond adequately to conventional treatment modalities^[2]
- Any significant contraindication for the use of systemic corticosteroids or other immunosuppressants^[2,11]
- Severe adverse effects requiring discontinuation of corticosteroids or other immunosuppressants^[12]
- Relapsing pemphigus, even at high doses of steroid^[13]
- As first line, in severe disease (along with systemic corticosteroids with or without other immunosuppressants).^[1,2,14]

Contraindications

- Known hypersensitivity to rituximab or other murine proteins^[11]
- Active severe infection^[15]
- HIV with CD4 <250 cells/mm³^[15]
- Severe heart failure^[7,11]
- History of bronchospasm, hypotension, and angioedema^[16]
- Pregnancy (FDA category C)^[3,5,10,17]
- Lactation.^[3,5,10,17]

Pregnant woman should be warned regarding the risks to the fetus. Women with childbearing potential should use effective contraception during treatment and continue the same for at least 12 months after the last dose.^[10]

The unknown risks to the infant from oral ingestion of rituximab should be weighed against the known benefits of breastfeeding. The existing evidence shows that the transmission of rituximab through breast milk to infant is very small, and guidelines do suggest normal immunization schedule for infants exposed to rituximab early in life.^[17,18] However, it is advised to regularly update with evolving evidence and guidelines in this area.

PRE-TREATMENT EVALUATION

The following investigations/ evaluations are mandatory before initiating rituximab:

- Complete hemogram, erythrocyte sedimentation rate, renal function tests, and liver function tests^[19,20]
- Serology for HIV (human immunodeficiency virus) infection, hepatitis B surface antigen, anti-HCV (hepatitis C virus) antibody, and anti-HBc (hepatitis B core) antibody^[19,20]
- Mantoux test, chest X-ray^[19,20]
- Cardiology evaluation, electrocardiography, and echocardiogram (if advised by a cardiologist)^[19,20]
- Estimation of immunoglobulin (Ig) G level in serum^[19,21]
- Baseline serum level of antidesmoglein 1 and 3 antibodies^[22]
- Ultrasound abdomen (if indicated clinically based on symptoms and clinical examination)
- Documented consultation by physician/pulmonologist and cardiologist to rule out contraindications such as active infections (including tuberculosis) and heart failure
- Vaccinations - Pneumococcal, tetanus toxoid, influenza virus, and hepatitis B vaccines are recommended at least 4 weeks before the initiation of treatment with rituximab. In patients with severe disease and who are receiving high-dose immunosuppressive drugs, the decision on vaccination should be made after weighing the advantage of prompt administration of rituximab against the benefit of receiving vaccination.^[15]
- Patients chosen for treatment with rituximab should avoid “live” vaccines such as oral polio, rubella (German measles), BCG, measles, oral typhoid, yellow fever, and the nasal flu vaccine immediately before and during treatment. If an emergent need for live vaccination arises while on treatment with rituximab, the former may be administered once the B-cell count returns to normal.^[10,15]
- Pneumocystis jirovecii pneumonia prophylaxis may be considered during and following treatment with rituximab^[10]
- Informed consent: Any doubts of the patient should be cleared before starting the treatment. The patient should be given adequate time to make an informed decision, except perhaps in an emergency. Written, signed, informed consent should be taken from all patients before starting the treatment. A patient information sheet should also be provided.

Most of these pre-requisites can be completed in outpatient clinic in patients with mild disease. This is applicable for subsequent infusions as well.

TREATMENT PROTOCOL

- Every patient should preferably be admitted and supervised closely in a day care treatment unit/intensive care unit/ward with facilities for close monitoring by a qualified medical practitioner^[21]

- Pre-hydration: 500 ml of 0.9% sodium chloride solution infusion^[11]
- Premedication: 100 mg intravenous methylprednisolone or its equivalent, 22.75 mg parenteral pheniramine maleate, and 500 mg of paracetamol per orally, 30 min before the infusion.^[18]

Dosing and interval

One gram on day 1 and 14 and then 500 mg at month 12 and every 6 months thereafter or based on clinical evaluation.^[18]

ADMINISTRATION OF RITUXIMAB

Preparation of the infusion

- 2 vials would provide 1 g/100 ml
- It is to be mixed with 400 ml of normal saline (after letting out 100 ml from the 500 ml bottle).

Infusion rate

Total quantity to be infused = 500 ml first infusion is started at a rate of 50 mg/h. If there is no evidence of infusion toxicity, infusion rate is incremented by 50 mg/h every 30 min to a maximum of 400 mg/h.^[18]

Infusion pump can improve the ease and accuracy of administration.

- 30 ml/h for 30 min (15 ml)
- 60 ml/h for next 30 min (30 ml)
- 90 ml/h till infusion is over (455 ml in 5 h)
- Total infusion period for the first infusion - 6 h.^[20]

Recommended total infusion time is 5–6 h for the first infusion

Subsequent infusions are administered at a rate of 100 mg/h, and in the absence of infusion reaction, the rate can be increased at 30 min interval by 100 mg/h to a maximum of 400 mg/h.^[18] These infusions will take 2–3 h.

Patient monitoring during infusion

- Check pulse, BP, and respiratory rate and do pulse oximetry every 30 min^[3]
- Watch for infusion reactions (fever, rigors, nausea, vomiting, headache, hypotension, and abdominal pain)^[23]
- On most occasions, infusion reactions can be managed by reducing the speed of infusion (half the flow rate and re-administer the premedication)^[11,23]
- Serious adverse effects such as angioedema and anaphylaxis require complete cessation of infusion^[19]
- Adequate hydration should be ensured immediately after infusion.

Follow-up

- Biweekly during the 1st month, once a month till 6 months after the 4th dose or complete withdrawal of steroids, whichever is later, once in 3 months for the next 1 year followed by once in 6 months for 1 year and once a year thereafter^[3]
- Complete hemogram every 3 months^[13]
- Repeat serology for antidesmoglein 1 and 3 antibodies at month 6, 12, and 24 and when there is clinical evidence of relapse^[3]

Treatment of relapse

European academy of dermatology and venereology (EADV) guideline suggests that a relapse that occurs during the tapering of systemic corticosteroid between month 0 and month 4 may be managed with increasing the dose of the latter. It is recommended to administer an additional cycle of 2 g of rituximab (1 g, 2 weeks apart), if the relapse occurs during the tapering of the systemic corticosteroid between month 4 and 6. In that case, the maintenance infusion of rituximab scheduled for 6th month will be avoided. No standard guidelines are available for the management of relapse that occurs after the withdrawal of the steroids and after the maintenance infusion of rituximab at month 6; hence, we recommend that a case-by-case approach may be adopted and systemic steroids may be resumed.^[3]

CONCLUSION

The treatment of pemphigus vulgaris and foliaceus has undergone a quantum change with the introduction of rituximab. After a few years of use in individual cases and publication of a few cases series, it has now gone through several randomized clinical trials. This drug is recently recognized as a first-line drug for the treatment of pemphigus vulgaris and offers prolonged drug-free remission.

Declaration of patient consent

Not required as there are no patients in this article.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Kidangazhiathmana Ajithkumar and Dr. Neelakandhan Asokan are on the editorial board of the journal.

REFERENCES

1. 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 (Ritux 3): A prospective, multicentre, parallel-group, open-label randomised trial. *Lancet* 2017;389:2031-40.
2. Schmidt E. Rituximab as first-line treatment of pemphigus. *Lancet* 2017;389:1956-8.
 3. Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, *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;34:1900-13.
 4. Weiner GJ. Rituximab: Mechanism of action. *Semin Hematol* 2010;47:115-23.
 5. FDA. FDA Approves Genentech's Rituxan (Rituximab) for Pemphigus Vulgaris. San Francisco, California: Genentech; 2018.
 6. Anandan V, Jameela WA, Sowmiya R, Kumar MM, Lavanya P. Rituximab: A magic bullet for pemphigus. *J Clin Diagn Res* 2017;11:WC01-6.
 7. Frampton JE. Rituximab: A review in pemphigus vulgaris. *Am J Clin Dermatol* 2020;21:149-56.
 8. Aksoy S, Harputluoglu H, Kilickap S, Dede DS, Dizdar O, Altundag K, *et al.* Rituximab related viral infections in lymphoma patients. *Leuk Lymphoma* 2007;48:1307-12.
 9. Highlights of Prescribing Information; 2021. Available from: <http://www.accessdata.fda.gov>labelpdf>. [Last accessed on 2021 Feb 04].
 10. British Association of Dermatologists Patient Information Leaflets (PILs). Available from: <https://www.bad.org.uk/ResourceListing.aspx?siteid=159&itemid=9741>. [Last accessed on 2021 Mar 28].
 11. Chen DM, Oduyungbo A, Csinady E, Gearhart L, Lehane P, Cheu M, *et al.* Rituximab is an effective treatment in patients with pemphigus vulgaris and demonstrates a steroid-sparing effect. *Br J Dermatol* 2020;182:1111-9.
 12. Cianchini G, Lupi F, Masini C, Corona R, Puddu P, de Pita O. Therapy with rituximab for autoimmune pemphigus: Results from a single-center observational study on 42 cases with long-term follow-up. *J Am Acad Dermatol* 2012;67:617-22.
 13. Reguiat Z, Tabary T, Maizieres M, Bernard P. Rituximab treatment of severe pemphigus: Long-term results including immunologic follow-up. *J Am Acad Dermatol* 2012;67:623-9.
 14. Scorer M, Setterfield JF, Harman KE. Rituximab with prednisolone as first-line treatment in pemphigus vulgaris. *Br J Dermatol*. 2020;182:1078-9.
 15. Leonardi CL, Hefferman MP, Gennifer GG. Rituximab and future biological therapies. In: Wolverton SE, editor. *Comprehensive Dermatologic Drug Therapy*. Edinburgh: Elsevier Health Sciences; 2013. p. 333-40.
 16. Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bittton A, *et al.* Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. *J Cutan Med Surg* 2019;23:50-74.
 17. Drugs and Lactation Database (LactMed). Rituximab. Bethesda, MD: National Library of Medicine; 2006.
 18. Hertl M, Zillikens D, Borradori L, Bruckner-Tunderman L, Burckhard H, *et al.* Recommendations for the use of rituximab (anti-CD20 antibody) in the treatment of autoimmune bullous skin diseases. *J Dtsch Dermatol Ges* 2008;6:366-73.
 19. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dorner T, *et al.* Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:909-20.
 20. Noormohammadpur P, Ehsani A, Mortazavi H, Daneshpazhooh M, Balighi K, Mofidi M, *et al.* Rituximab therapy improves recalcitrant pemphigus vulgaris. *EXCLI J* 2015;14:109-16.
 21. Lymphoma Action, Rituximab for Lymphoma; 2021. Available from: <https://www.lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma-antibody-therapy-including-rituximab/rituximab-lymphoma>. [Last accessed on 2021 Mar 21].
 22. Müller R, Hunzelmann N, Baur V, Siebenhaar G, Wenzel E, Eming R, *et al.* Targeted immunotherapy with rituximab leads to a transient alteration of the IgG autoantibody profile in pemphigus vulgaris. *Dermatol Res Pract* 2010;2010:321950.
 23. Can M, Alibaz-Oner F, Yilmaz-Oner S, Atagunduz P, Inanc N, Direskenil H. Accelerated infusion rates of rituximab are well tolerated and safe in rheumatology practice: A single-centre experience. *Clin Rheumatol* 2013;32:87-90.

How to cite this article: Ajithkumar K, Johny S, Salim P, Asokan N. Rituximab in pemphigus vulgaris - Standard operating procedure. *J Skin Sex Transm Dis* 2022;4:236-9.