Viva Voce

Rituximab in the treatment of Skin Diseases

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What is Rituximab and what is its Mechanism of Action?

Rituximab, as its name suggests, is an Ig G 1 kappa monoclonal antibody and is chimerically composed of murine variable region (Fab portion) that is fused with the human constant portion (Fc portion). The Fab portion primarily binds to the CD20 antigen, located exclusively over the pre-B (hematopoietic) and mature B lymphocytes (peripheral) and not the hematopoietic stem cell precursors.[1] This allows the B cell regeneration from these unaffected hematopoietic precursors as well as continued production of immunoglobulins from plasma cells. It primarily targets CD20 cells, however some degree of targeting of CD19 also occurs, though not to a major extent. Once bound, the Fc portion of Rituximab recruits the immune effector cells that mediate the lysis of the CD20+ B lymphocyte through complement dependent cytotoxicity,[2] antigen-dependent cell-mediated cytotoxicity, and apoptosis.[3] B-cell regeneration into peripheral circulation has been shown to occur 6–12 months posttherapy, and serum immunoglobulins have not been demonstrated to decrease significantly.[4–9]

There is a very mild effect of rituximab on activated T cells also. Since most autoimmune diseases do involve T cells activation as a peripheral pathway, rituximab action here is an added advantage. It reduces the production of T cell modulating cytokines and interfere with presentation and processing of autoantigens besides decreased activation of the autoreactive T cells.[10] However, this action is not significant enough to produce immunosuppression due to T cell inactivation.

What are the Indications of Rituximab?

Rituximab has been Food and Drug Administration approved in CD20+ B cell non-Hodgkin’s lymphoma and treatment-resistant rheumatoid arthritis. The off-label uses where rituximab has been used earlier are as enumerated in Table 1.

- Traditionally, the indications of rituximab in pemphigus are[28]
- Those patients who fail to respond adequately to conventional treatment
- In those in whom systemic corticosteroids are contraindicated or have to be discontinued on account of side effects
- Relapsing pemphigus following treatment with conventional drugs.

With the available data, more recently, it has been used as the first-line therapy in patients with severe disease.[29] I would prefer that we understand the drug well and use it as first-line rather than after other drugs have failed. I make this point also because I am not keen on giving the drug to someone who has already been broadly immunosuppressed. In such situations, the chances of side effects such as infection are higher.

- As a combination therapy with immunoabsorption, rituximab has resulted in rapid clearance and long-term control of difficult to treat cases of pemphigus[30]
- Efficacy and safety of rituximab are maintained when it is readministered during relapses.[31]

What are the Indications where you have Used Rituximab in your Practice?

I have used it in pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus, and vegetans – all pemphigus variants successfully. I have also used it both as first-line and second-line therapy in bullous pemphigoid. I have used the drug widely in vasculitis, especially ANCA-associated vasculitis and rheumatoid vasculitis. I did use the drug in one case of epidermolysis bullosa

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acquisita, but the response was very partial. I have also used it in scleroderma-associated interstitial lung disease and systemic lupus erythematosus.

**What are the Contraindications to the Use of Rituximab?**

- There are actually no absolute contraindications to the use of rituximab provided you are an expert at handling the drug in clinical practice. Theoretically, hypersensitivity to rituximab or other murine proteins and severe cardiac failure are absolute contraindications. Hepatitis is a relative contraindication. Even sepsis, human immunodeficiency virus infection (>250 cell count) and tuberculosis are not absolute contraindications.
- It is not recommended in childhood mainly because of limited clinical experience but has been used with no long-term adverse effects in cases where benefits outweigh the risks.\(^{[12-37]}\)
- It is not recommended in pregnancy and lactation (Category C).\(^{[38]}\) Contraception of 1 year is advised to all female patients receiving rituximab.\(^{[39]}\)

**What is the Protocol and Dosing Recommended for Dermatological Disorders? Does the Dosing/Protocol Vary as per the Disease Condition Treated/or the Severity of the Disease?**

There are two broadly accepted protocols for the drug in adults – the RA protocol and the lymphoma protocol. In the former, the drug is given as an infusion of 1 gm every two weeks for two doses. In the latter, the drug is given at 375mg/m² body surface area doses every week for 4 weeks.

The dosing need not vary according to the severity of the disease. However, I have had pemphigus patients who did not respond well to the protocol. When we checked for CD20 cells by flow cytometry, we found that the numbers of cells destroyed were not significantly decreased. This helped me to administer up to two additional doses. This is done only when the disease is severe enough to warrant it, and there is no other way out. We do not know the long-term side effects of the drug over say 15 years. Another instance when a booster of the drug is given is when there is a relapse of the disease in spite of the patient being on interval immunosuppresses with drugs such as azathioprine or mycophenolate mofetil.

Rituximab has also been used as a combination therapy with IV Ig,\(^{[40]}\) immunoadsorption,\(^{[41]}\) and pulsed dexamethasone with other immunosuppressants such as azathioprine/mycophenolate mofetil.\(^{[41]}\)

**How to Counsel a Patient for Rituximab? Is it Covered Under Medical Insurance?**

In dermatology, most biologicals are not covered by insurance. During counseling, it is important to teach the patient about the disease, how the drug works, and the need for very close monitoring. We also need to educate the patient that arrhythmias and infusion reactions can occur and therefore need monitoring.

**Can you Share a Checklist of all the Investigations to be Performed before the Administration of Rituximab?**

Complete medical examination; complete blood counts; chest X-ray; ultrasonography of abdomen; renal and liver functions, HIV, HBsAG, HBC core total antibody, anti HCV antibodies, and an Electrocardiogram (ECG) are the basic investigations I would do in every case. Additional investigations would be done as the situation demands.

**Can Rituximab be Administered to Individuals with a Previous History of Tuberculosis?**

Yes.

**Can Rituximab be Administered Concurrently with other Immunosuppressants?**

Preferably not, but can be followed by other immunosuppressives.
Can rituximab be administered in patients with hepatitis B/hepatitis C?

Hepatitis B requires prophylactic therapy. If viral load at detection is high before starting therapy, I would avoid rituximab until the viral load comes down. As for hepatitis C, I do not give rituximab though there are reports that the drug can be used guardedly.[42]

Can rituximab be administered in HIV-positive individuals who are adequately suppressed with antiretroviral therapy?

Yes, keep a watch on the CD4 counts though.

How is rituximab available? How is it administered? Can it be administered in a daycare setting? What are the parameters to be monitored while administering rituximab? How long is the hospital stay required?

Rituximab is available as a 50 ml vial of liquid containing 500 mg of the drug to be infused. It is mixed with 450 ml saline to create a concentration of 1mg/ml. The infusion rate is 50 ml/h in 1½ h and increased by 50 ml every ½ h till you finish the infusion. Maximum infusion rate is 400 ml/h and the total infusion time would be 5–6 h. It is preferable to admit for a day, though many doctors use it in day-care setting. I advise strongly against this as infusion reactions can be seen up to 24 h after the infusion is over. Monitor the vitals, pulse oximetry. Do not forget to give premedication with hydrocortisone 100 mg and pheniramine maleate 22.75 mg intravenously before each infusion.

For subsequent infusions, the dose is 100 ml/h with a 30 min escalation of 50 ml/h to a maximum infusion rate of 400 ml/h.

What is the cost of medication?

In hospitals, 500 mg vial of rituximab costs approximately Rs. 35,000.

Does the biosimilar vary in its efficacy and safety versus the original?

This question is wrong. What you get in India is an intended biosimilar. Biosimilarity has not been proved in clinical trials.

What are the short-term and long-term adverse effects seen with rituximab? Which are the ones that you have encountered in your practice?

The side effects that have reported to occur with rituximab are as in Table 2.

Look for cytopenias—both immediately and delayed. The others are rare. I have not seen them in my practice. Of course, I have encountered infusion reactions and arrhythmias in about ten patients over the last 10 years.

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