Editorial

Rituximab in pemphigus

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Pemphigus is a chronic, muco-cutaneous autoimmune blistering disorder; two main variants being pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is the most common subtype, varying between 75 to 92% of total pemphigus patients.[1,2] Although no community based studies are undertaken to estimate the incidence of pemphigus in India, it is relatively common. A questionnaire based survey in Thrissur district of south India estimated pemphigus incidence to be 4.4 per million population.[3] Mortality due to pemphigus has decreased remarkably with the aggressive and widespread use of corticosteroids, prior to which it was as high as 90%. High dose corticosteroids were once used in combination with other immunosuppressants with good improvement, but such high doses of corticosteroids were often associated with severe side effects, and were responsible for the death of nearly 10% of the patients.[4] With the aim of reducing the adverse effects of long term, high dose steroid administration dexamethasone cyclophosphamide pulse (DCP) therapy was introduced in 1984.[5] Since then DCP or oral corticosteroids with or without adjuvant immunosuppressants (azathioprine, cyclophosphamide, mycophenolatemofetil, and cyclosporine) have been the corner-stone of therapy for these disorders in India.[6,7] Despite the benefits associated with DCP therapy compared to high dose oral steroids, it cannot be denied that even DCP therapy with or without adjuvants can lead to numerous adverse events, which account for majority of deaths in pemphigus.[8] Moreover there are few patients who fail to improve with these conventional treatments or have contraindications for their usage. Thus there has been a constant search for newer therapeutic modalities in pemphigus. Rituximab (Reditux. Dr. Reddy's, Hyderabad, India and MabThera™, Roche, Basel, Switzerland), a monoclonal chimeric IgG1 antibody targeting the B cell specific cell-surface antigen CD20, is one such newer novel therapy for pemphigus (an off-label indication for its use. It has so far been approved by FDA for use only in CD 20+ B cell non-Hodgkin's lymphoma, treatment resistant rheumatoid arthritis, Wegener's granulomatosis and microscopic polyangiitis).

HOW DOES RITUXIMAB ACT?

The human B-lymphocyte-restricted differentiation antigen Bp35 (CD20), is a cell surface non glycosylated hydrophobic transmembrane phosphoprotein of 35kDa molecular weight, and appears to function as a component or regulator of a voltage-independent calcium channel.[9] CD 20 is expressed on the surface of B cells from pre-B-cell through memory B-cell stages but neither on stem cells and pro B cells nor on plasma cells. Rituximab is a chimeric monoclonal antibody directed against CD20 and acts by causing death of CD 20 positive cells by complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.[10] Apoptosis of CD 20 positive cells is also believed to play a role.[11] Thus rituximab leads to depletion of mature B lymphocytes which would transform into antibody producing short lived plasma cells. But stem cells and pro B cells are not affected as they do not express CD20 cell surface molecule and these cells reconstitute the B cell population after 6 months to 1 year.[12]

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USE IN PEMPHIGUS

Heizmann *et al*, used rituximab for the first time in treatment of autoimmune bullous diseases and reported a case of paraneoplastic pemphigus successfully treated by rituximab.[13] Subsequently many authors have used rituximab in the treatment of various immunobullous diseases including PV[14] and PF.[15]

Indications

Rituximab is indicated in pemphigus patients who fail to respond adequately to conventional treatment modality, or in whom systemic corticosteroids and/or other immunosuppressants are contraindicated or cause severe adverse effects requiring its discontinuation.[16,17] Rituximab is also indicated in patients who relapse following treatment with conventional drugs.[18] Few authors, including us have used rituximab as a first line treatment especially in patients with severe disease.[19-22]

Contraindications

Contraindications to rituximab include hypersensitivity to rituximab or other murine proteins, active severe infections, HIV infection with CD4 cell count $<250/\mu l$ and severe heart failure.[16,23]

Use in special situations

Children: Currently use of rituximab is not recommended in children, mainly because of limited clinical experience in this age group.[16] Few authors, including us have used rituximab in childhood pemphigus with no long term adverse affects.[19,20,24-27] It is essential to weigh the benefits of the drug with potential adverse affects in pediatric age group.

Pregnancy and Lactation: Rituximab is not recommended in pregnancy or lactation (FDA Category C). A recent review of pregnancy outcomes from the rituximab global drug safety database identified 231 cases of pregnancy associated with maternal rituximab exposure. Of 153 pregnancies with known outcomes, 90 resulted in live births, 33 ended in spontaneous abortion, with one stillbirth at 20 weeks' gestation (umbilical knot) and 28 elective terminations. Twenty-two of the live births had abnormalities at birth; four neonatal infections and two congenital malformations were reported.[28] Contraception for one year is advisable to all female patients receiving rituximab.[23]

TREATMENT PROTOCOLS

There is currently no consensus on the optimal dosage and schedule of rituximab in treatment of pemphigus. The various treatment protocols followed include:

1. Lymphoma protocol- Most commonly followed protocol. Rituximab is administered at a dose of 375mg/m^2 body surface area weekly for four weeks.[20,29-31]
2. Rheumatoid arthritis protocol- Two doses of rituximab 1g is administered at an interval of 15 days. Increasingly used by dermatologists and is the protocol currently followed in our institute.[18,19,32] Advantage over the lymphoma protocol include less cost and fewer infusions.
3. Combination therapy- Rituximab has been used in combination with IVIG,[33] immunoadsorption[34] and dexamethasone pulse therapy[34]
4. Long-term rituximab treatment with regular infusions every 4 or 12 weeks following an induction cycle of infusions every week[17]

SCREENING, PRE-MEDICATION AND RITUXIMAB ADMINISTRATION

Pre-rituximab evaluation should include:

- Complete haemogram
- Liver function tests
- Renal function tests,
- Chest X ray, Mantoux test, HRCT (when indicated)
- Screening for viral infection including- HBsAg, anti-HBc, anti- HCV, HIV-1 and HIV-2
- ECG and echocardiography

Few authors also recommend pre-treatment assessment of baseline immunoglobulin (Ig) levels as reduced baseline level of IgG is a risk factor for severe infections with rituximab.[23,35] In our experience acute infections are rare and occur in patients with active disease and raw erosions. Once the erosions are healed the risk of infection is negligible and thus baseline Ig levels are not done regularly in our patients.

Pre-medication and rituximab administration

Pre-medicate with hydrocortisone 100mg intravenous (IV), pheneramine maleate 22.75mg IV and paracetamol 500mg oral 30 minutes (min) prior to infusion. First infusion is administered at a rate of 50mg/h IV, escalated every 30min by 50mg/h to a maximum

infusion rate of 400mg/h, total infusion time: 5–6h. Subsequent infusions are initiated at 100mg/h, with a 30-min escalation of 50mg/h to a maximum infusion rate of 400mg/h.

EFFICACY IN PEMPHIGUS

Currently no randomized control studies are available comparing the efficacy of rituximab to conventional treatment modalities. Most of the data available regarding its use are from large case series and prospective open labeled trials. Review of patients with pemphigus treated with rituximab showed that 98% of PV patient responded to therapy with 40% having complete remission. Success rates were even better with PF with 100% responding to therapy and 40% having complete response.[22] Among patients with various autoimmune disorders treated with rituximab, patients with pemphigus had the greatest improvement in well-being.[36] Ahmed *et al,* treated 11 treatment resistant PV patients with two cycles of rituximab (375mg/m^2 of body-surface area) once weekly for three weeks and intravenous immune globulin (IVIG) (2g/kg of body weight) in the fourth week, followed by a monthly infusion of rituximab and IVIG for 4 consecutive months. The authors reported complete remission (CR) off all treatment in nine patients lasting 22 to 37 months. Two patients with recurrence were treated with rituximab only and achieved sustained remission.[33] Cianchini *et al,* treated 12 patients of pemphigus (10 PV and 2PF) according to the lymphoma protocol and reported CR in nine patients and partial remission (PR) in three patients. No relapses were seen during the follow up period ranging from 6-18 months. Patients with PR were treated with additional rituximab.[30] Later using a similar treatment schedule, Joly *et al,* reported their experience of treating 21 patients who were resistant to conventional therapy or had frequent relapses. Eighty six percent of patients achieved CR within three months and relapse was seen in nine patients after a mean of 18.9 months. After a median follow up period of 34 months 86% of patients were free of disease.[29] Similar outcomes were reported by Kasperkiewicz *et al,* with 9 of 10 patients of pemphigus achieving CR.[37] The same authors have also reported use of rituximab in combination with immunoadsorption, pulsed dexamethasone and azathioprine /mycophenolate mofetil in 23 patients with a long-term complete remission in 83% of cases.[34]

Recently we reported 10 patients of pemphigus treated with rituximab. It was given as per its protocol for use in rheumatoid arthritis. Eight patients had achieved CR and one patient had PR.[19] The control of disease activity was achieved in most of the patients within 8 weeks of rituximab administration. At the time of sending the manuscript to the journal follow-up of 6-12 months was available. This follow-up has now extended to 12-18 months and no relapses are seen. The patient with PR was subsequently treated with an additional dose of rituximab and now she has achieved CR. Similar findings were later reported by Matsukura *et al,* in their series of nine patients, four patients achieved CR and PR were seen in the rest. Relapses were observed in four patients between 5 and 13 months after rituximab treatment and were treated with additional rituximab infusions.[18]

Two long term studies have provided valuable data on efficacy and safety of rituximab in treatment of pemphigus.[20,32] Reguiai *et al,* treated 13 patients with rituximab according to the lymphoma protocol, nine achieved CR three months after the first rituximab cycle. Thereafter, seven patients (four with maintenance therapy) relapsed within a mean of 18 months and were treated with one or two additional rituximab cycles. With mean follow-up at 41 months after the first rituximab cycle and 28 months after the last one, all 13 patients were in CR.[20] Cianchini *et al,* treated 42 patients of pemphigus (37 PV, 5PF) with two doses of rituximab, 36 of 42 patients (86%) achieved a CR and discontinued steroids within six months. Six patients had CR off therapy with an additional infusion of rituximab six months after initial treatment. Twenty patients experienced a total of 34 relapses; the time to relapse was 8 to 64 months. Every relapse was treated with rituximab (500mg) without corticosteroids, which induced a new CR.[32] Although no head to head comparative studies have done comparing these two protocols, the reported efficacy of the rheumatoid arthritis protocol is comparable to the lymphoma protocol. Rheumatoid arthritis protocol has added advantage of low cost and fewer infusions. Recent open labeled study using low dose rituximab (two doses of 500 mg 15 days apart) had similar long term outcome as other studies where full dose was used.[38] This would further cut the cost of therapy. Currently a randomized control trial comparing long term outcome between low dose and full dose rituximab is under way at our center.

ADVERSE EFFECTS

Infusion related reactions occur in 10% of patients receiving rituximab.[22] There are no phase II prospective trials evaluating the adverse effects of

rituximab in pemphigus patients and most of the data on safety is from studies on lymphoma and rheumatoid arthritis patients. The most frequent infusion related side effects include fever and rigor.[39] Others being flu-like symptoms, nausea, vomiting, abdominal pain, and hypotension. Treatment related side effects occurred most frequently at the first antibody infusion (65%) and less often during the second (15%), third (5%), and fourth (5%) infusions. [39] Data from national registry on safety of rituximab in patients with different autoimmune diseases, in which pemphigus patients constituted 10% of treated cases; reported infusion related reactions in 5.9% of patients.[36] Many of these reactions are mild and only require reduction in the infusion rate.[39] Serious side effects like anaphylaxis and angioedema, requiring cessation of infusion can also occur.[19] Two of the patients in our series had developed angioedema, one requiring cessation of infusion. Both the patients are presently in CR and are in good health. The incidence of serious infections is 5.3 per 100 patient-years and most of them occur within seven months of infusion.[36] Infections are the major cause of death and are mainly bacterial, opportunistic infections are infrequent.[36] The serious infections reported in pemphigus patients include bacterial sepsis, bacterial pneumonia, pyelonephritis, *Pneumocystis carinii* pneumonia, bacterial arthritis, cytomegalovirus gastritis, *Listeria monocytogenes sepsis*, varicella zoster infection and cutaneous *Mycobacterium chelonae* infection.[22] Most of these infections occurred in patients who had been treated with other immunosuppressive medications. Cutaneous adverse effects like rash, exfoliation[39] and vasculitis[40] have also been reported. Toxic epidermal necrolysis has occurred in rhesus macaques after administration of rituximab.[41] There has been one case report of Stevens-Johnson syndrome associated with rituximab.[42] Urticaria is a common side effect of rituximab; incidence in non-randomized trials ranged from 3 to 14%.[43] Cardiovascular complications like sinus tachycardia, dysrhythmia and myocardial ischemia can occur and are more common in patients with pre existing conduction abnormality or heart failure.[39] Such patients require careful monitoring during and after infusion. Progressive multifocal leukoencephalopathy (PML) a JC virus infection of the brain has been reported in patients receiving rituximab.[44,45] Such adverse effects are rare and were seen in less than 1:20 000 treated rheumatoid arthritis patients.[23] PML has not been reported in rituximab treated pemphigus patients. Cianchini *et al*, reported parkinsonism in a patient 12 months after the last dose of rituximab, however it is not clear whether the drug was directly involved in causing the disease.[32] Few studies have reported no enhanced rates of solid malignancies or lymphoma under rituximab treatment.[46,47] An open-label extension trial of 1,039 patients treated for RA, made note of new malignancies occurring during treatment with rituximab.[48] The current evidence gives no evidence for or against increased incidence of malignancy associated with rituximab. In our experience early infusion related reactions are common and are managed by decreasing the infusion rate. Severe infections are rare and are commonly seen in patients with extensive erosions. Most of them can be managed by appropriate antibiotics. There appears no increased risk of infections once the erosions have healed. However it should be emphasized that these adverse effects should not inhibit the physician from using the drug, as any therapy is associated with its potential side effects. On the other hand these patients should be kept under close and long term follow-up for early detection of any such complications.

Management of adverse reactions

In immediate reactions, treatment should be discontinued. If possible, after waiting for 30 minutes, rituximab infusion can be continued at a slow rate (half flow rate). Cortisone and antihistamines should be re- administered. Rituximab therapy should be discontinued in the following situations: (a) severe infections (b) serious complications, e.g., anaphylactic reaction in patients who do not tolerate mouse proteins, and (c) pregnancy.[16]

THE WAY FORWARD

Although the current studies have established the role of rituximab in the management of treatment resistant pemphigus, there is still a lack of consensus on certain aspects. Different authors have used different treatment protocol in combination with various immunosupressants. There is no consensus on the dose of rituximab to be used, the interval between the infusions and indication for repeat infusions. Long term prospective studies are required to answer these issues. Rituximab is currently indicated only when conventional treatment modalities fail or are contraindicated. In future with better information on efficacy and safety profile and more wide spread use rituximab can become a first line therapy, especially in patients with severe disease or patients who wish to avoid use of long term immunosupressants.

CONCLUSION

Currently there is adequate data establishing the efficacy of rituximab in treatment of pemphigus. Majority of the patients show clinical improvement within two-three months of rituximab administration and intervening corticosteroids can be tapered rapidly during this period. Fifty to sixty percent of patients achieve CR with one infusion cycle and have no relapses. Around 40-50% patients will have one or more relapses and can be treated with small doses of corticosteroids or repeat infusions of rituximab. It should be emphasized that patients who have failed to respond to conventional therapies or patients with severe disease who are known to respond poorly to these treatment also show good response to rituximab.[1,19,49] Although rituximab appears expensive, it has the advantage of fewer hospital admissions (just two infusions in majority of patients), rapid tapering of other immunosupressants and minimal long term adverse effects. In comparison, in conventional treatment modalities the duration of treatment is long, extending for two-three years. If DCP is administered, the patients need repeated hospitalization for three days in a month, with subsequent loss of employment and income. Such long term immunosupression is also associated with its complications and side effects like osteoporosis, avascular necrosis, cataract, obesity, hirsutism and cost associated with their management goes unaccounted. The patients are required to adhere strictly to the DCP protocol and such long term compliance is rarely seen among patients. There is however no head to head comparison studies of rituximab with DCP. Few puritans feel that larger studies and economic evaluations comparing conventional therapy and rituximab are needed for a more evidence-based answer, especially the benefits of never needing high dose corticosteroids. As rituximab has established its place in management of pemphigus, we feel there is no need to carry out studies to compare DCP with rituximab. It may be unethical to deprive a patient of a drug which is effective. There is no doubt that DCP therapy has made its place in management of pemphigus in India. However, one needs to move ahead with times and use newer therapies. Rituximab is a step in that direction. Infact we are so impressed with efficacy of rituximab that we have started using it as a first line therapy in pemphigus patients. It is very gratifying and satisfying to see patients with extensive skin and oral involvement coming for follow up and telling the physician that they are completely okay.

Since our initial report we have now more than 40 patients (including children) who have received rituximab and are doing well. Infact as our results are quiet impressive the number of patients who are coming to us for treatment have increased. The senior author would like to express sincere thanks to Dr.Neil Shear from Sunny Brook University, Toranto, Canada who initiated us to use rituximab in pemphigus. To emphasize the usefulness of rituximab in pemphigus, Dr. Neil said “Rituximab acts like putting water on fire in pemphigus” and today we realize how true these words are. Infact he told us to use this protocol (rheumatoid arthritis) in pemphigus. So far it has done very well and hopefully in near future it would be the best therapy for treatment of pemphigus. When it comes to saving a human life, cost is secondary. Through this editorial we would like to tell and encourage our fellow colleagues to use rituximab in pemphigus. It does work and indeed works very well. We would also like to thank Prof. Takashi Hashimoto and his faculty from the University of Kurume, Japan for carrying out the immunological studies. Finally and above all our thanks to Dr. Reddy’s Pharmaceuticals, Hyderabad, India for providing rituximab free of cost to poor patients. No words can describe their contribution.

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