# Rituximab

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Rituximab is a chimeric mouse-human monoclonal antibody against the CD 20 antigen on the surface of B lymphocytes. It binds to CD20 and causes B cell death by antibody dependant cell-mediated cytotoxicity, complement mediated cytotoxicity and apoptosis. It leads to rapid and sustained depletion of B cells. It is licensed for use in adults with CD20 positive B-cell lymphoma and rheumatoid arthritis. In children, it has been used in a variety of off-label indications with promising results. It has proved useful as salvage therapy in relapsed refractory non-Hodgkin's lymphoma and leukemia, and in hematological conditions including chronic immune thrombocytopenic purpura, hemophilia with inhibitors, and autoimmune hemolytic anemia. It has also proved effective in autoimmune conditions like primary systemic vasculitis and systemic lupus erythematosis. Nephrotic syndrome and opsoclonus-myoclonus syndrome are among the emerging indications for rituximab. In solid organ transplantation, rituximab is useful in the prevention and treatment of acute and chronic rejection as well as in post transplantation lymphoproliferative disease. Toxicity includes acute infusion reactions, susceptibility to bacterial infections, and reactivation of viral infections.

**Key words**: *Rituximab, Monoclonal antibodies, CD20.*

Conventional chemotherapy has dose limiting toxicity as these drugs kill normal cells in the body along with cancer cells. Constant untiring efforts in an attempt to design newer drugs that will aim at killing only malignant cells while sparing normal bystanders have ushered in the era of targeted therapy. Targeted therapy includes monoclonal antibodies and small molecule inhibitors. These drugs target the antigens, proteins or enzymes that are unique to cancer cells or are expressed at high levels by cancer cells, leading to a cascade of events that destroy the target cell. Rituximab, the first monoclonal antibody discovered in 1991, entered human phase I trials in 1993 and was licensed for the treatment of relapsed CD20 positive low grade lymphomas in adults in November 1997. It is currently licensed for treatment of all CD20 positive non-Hodgkins lymphomas in adults and for active rheumatoid arthritis not responding to anti-TNF therapy.

## STRUCTURE AND MECHANISM OF ACTION

Rituximab is a genetically engineered recombinant chimeric mouse-human monoclonal antibody (IgG1-k) against CD20, a transmembrane protein of uncertain function found on pre-B and mature B lymphocytes.

The chimeric structure of rituximab comprises human IgG-1 and variable regions from a murine antibody to CD20. The murine regions selectively bind to the CD20 antigen expressed on the surface of both normal and malignant B lymphocytes. The human region allows rituximab to bind to Fc receptors on effector cells. Once bound to CD20, rituximab causes B-cell death by a variety of mechanisms including antibody dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and apoptosis. Thus it causes rapid depletion of CD20-positive B cells. CD20 is an ideal target for monoclonal antibody therapy because it is found exclusively on B cells, is not shed from B cells and is expressed at high levels.

In lymphoma, in addition to destroying CD20 positive tumour cells, rituximab increases sensitization to chemotherapy, by down regulation of anti-apoptotic proteins and signaling pathways suggesting that rituximab-chemotherapy combinations have additive effects [1]. In autoimmune disorders, rituximab leads to a reduction in pathogenic antibody production through B cell depletion and also modulates T cell function [2]. In solid organ transplantation, mechanisms include decrease of pathogenic B cell clones with decrease in pathogenic (auto) antibodies and decreased antigen-presentation with decreased activation of pathogenic T cell clones [3].

## PHARMADYNAMICS AND PHARMACOKINETICS

Rituximab binding is seen exclusively in lymphoid cells in the tumour tissue, thymus, spleen, lymph nodes and peripheral blood. Serum levels and half life after rituximab are proportional to the dose and tumour burden. Age and sex do not have any effect on the pharmacokinetics of rituximab. Its pharmacokinetics in patients with renal and hepatic impairment has not been studied. Rituximab does not show interactions with other drugs used in combination. Studies in primates show that rituximab does cross the placental barrier but does not cause any teratogenicity. Anecdotal reports of rituximab use in humans during pregnancy have resulted in normal healthy offsprings with B cell depletion that returns to normal by 4 months of age. Rituximab is secreted in breast milk and hence is to be avoided during lactation. The safety of immunization with live viral vaccines following rituximab has not been studied and is presently not recommended for 6-9 months following rituximab.

## USES

Rituximab is currently licensed for use in CD20 positive lymphoma and rheumatoid arthritis in adults. It has been used in several other off-label indications in children with promising results (***Table* 1**).

*CD20 positive non-Hodgkins lymphoma (NHL) and acute lymphoblastic leukemia (ALL)*: Treatment with rituximab along with chemotherapy is now considered standard of care in adults with CD20 positive NHL. Pediatric mature B-cell lymphoma/leukemia (Burkitt's lymphoma and diffuse large B cell lymphoma (DLBCL) are positive for CD20, hence are amenable to treatment with rituximab. Studies have shown that rituximab, when used either as single agent or in combination with chemotherapy as salvage therapy for relapse or refractory NHL has shown response rates of 60 to 80% [4,5]. In relapsed refractory precursor B cell ALL, the response to rituximab has been encouraging.

A phase II study of rituximab in newly diagnosed mature B cell NHL in children, using a single dose of rituximab of 375 mg/m$^2$ reported a 42% response rate. In this study conducted by the Children's Oncology Group (COG), 2 to 4 doses of rituximab (375mg/m$^2$) were added to the chemotherapy backbone in children with advanced stage mature B cell NHL. There was only one grade-3 allergic reaction among 237 infusions of rituximab. There was no increase in mucositis or infections [6]. A phase III randomized study is ongoing to determine if addition of rituximab to the chemotherapy backbone improves event free and overall survival. The results of this study could be pivotal in proving the role of rituximab in frontline treatment of B cell lymphoma- leukemia in children.

*CD20 positive Hodgkins lymphoma (HL)*: Rituximab has proven role in nodular lymphocyte predominant Hodgkins lymphoma (NLPHL) and relapsed classic Hodgkins lymphoma in adults [7,8]. In children its use for NLPHL is anecdotal and awaits further clinical trials.

**TABLE I** INDICATIONS WHERE RITUXIMAB IS PROVED EFFICACIOUS IN CHILDREN

| Condition | Level of Evidence (References) |
|---|---|
| CD20 positive NonHodgkins lymphoma | Ia (4,5) |
| Chronic immune thrombocytopenic purpura | IIa, IIb (9,10,11) |
| Autoimmune hemolytic anemia | IIa (13) |
| Systemic lupus erythematosus | III (20,21) |
| Nephrotic syndrome | IIa (22) |
| Post transplant Lymphoproliferative disease | III (25) |
| Renal transplantation | Ib (26) |

*Chronic immune thrombocytopenic purpura (ITP)*: Several series of children with chronic ITP refractory to multiple prior treatments treated with rituximab have been reported [9-11]. The response rates range from 30-70%. Most of the responses were obtained within 4 weeks and were maintained for a year. Some children needed retreatment for relapse at around 1 year. Rituximab in the dose of 100 mg or 375 mg/$m^2$/week adminis-tered four times is now among the recommended treatment strategies for children with chronic ITP [12].

*Autoimmune hemolytic anemia (AIHA):* AIHA in childhood can be a primary autoimmune disease or it can be secondary to immunodeficiency, malignancy or infection. First line treatment is with high dose steroids followed by immunosuppressants and splenectomy, which have limited efficacy.

Cohort studies have described the use of weekly rituximab for AIHA in a total of 25 children, all of whom had failed conventional treatments with 92% children having a complete sustained response for 7-28 months [13,14]. It has also proved useful in the treatment of autoimmune hemolytic anemia in the setting of Evan's syndrome, SLE and autoimmune lympho-proliferative syndrome [15-17].

*Hemophilia with inhibitors*: Patients with hemophilia who develop inhibitory antibodies to factor VIII and IX, need treatment with bypassing agents for acute bleeds and immune tolerance therapy to eliminate the inhibitors. Rituximab has been used for treating hemophiliacs with inhibitors with upto 63% response. A national cohort in the UK suggested the use of rituximab combined with factor VIII as potentially useful treatment for patients with inhibitors resistant to standard immune tolerance [18].

*Primary systemic vasculitis (PSV)*: Primary vasculitic syndromes include Henoch-Schonlein purpura (HSP), Kawasaki disease (KD), polyarteritis nodosa (PAN), Takayasu disease (TD) and the ANCA-associated vasculitides (AAV). The current first line treatment for severe PSV (excluding KD and HSP) includes therapy with corticosteroids and cyclophosphamide, sometimes needing plasmapheresis. Use of rituximab has pro-ved beneficial in the treatment of the PSV conditions with lesser toxicity and enduring remissions [19].

*Juvenile idiopathic arthritis (JIA)*: Rituximab was approved for treatment of rheumatoid arthritis in adults in 1998 but its usefulness in the treatment of children with severe refractory JIA is anecdotal and limited.

*Systemic lupus erythematosus (SLE)*: Childhood-onset systemic lupus erythematosus (SLE) a multisystem autoimmune disease associated with severe hematologic and renal involvement, has been treated with rituximab [20].

In the largest long-term experience in children treated with rituximab for severe SLE, Nwobi, *et al*. have reported over 90% response rate in lupus nephritis with control of proteinuria and a fall in auto antibodies [21].

Kumar, *et al*. [16] have reported a series of 9 patients with pediatric SLE related autoimmune thrombocytopenia (AITP) and autoimmune hemolytic anemia (AIHA) with 100% of the patients responding to rituximab with median time to remission being 2-4 weeks. Complete B cell depletion was seen in all patients for a prolonged period but without any serious infections.

*Nephrotic syndrome*: Rituximab has been used in the treatment of frequently relapsing steroid or cyclosporine dependant or resistant nephrotic syndrome patients, who needed intensive multiple agent immunosuppressive therapy [22,23].

In the French multicenter trial, of the 22 patients with long standing steroid dependant nephrotic syndrome treated with rituximab, 15 were proteinuria-free at the time of rituximab use and the remaining 7 patients were nephrotic. Of the 7 nephrotics, 3 achieved remission with the addition of rituximab. One or more immunosuppressive treat-ments could be withdrawn in majority of the patients and complete withdrawal was achieved in 23% patients. Thus, rituximab was effective in all patients when administered during a proteinuria-free period in association with other immunosuppressive agents.

In patients with steroid resistant nephrotic syndrome, mostly with focal segmental glomerulosclerosis (FSGS), the response rate to addition of

rituximab to ongoing immunosuppressive therapy was 80%. It has also been used in treatment of recurrent FSGS after renal transplantation.

*Neuromuscular disorders*: Rituximab has been successfully used in many autoimmune neurological disorders in adults. In children opsoclonus-myoclonus-ataxia syndrome (OMS), may be idiopathic or secondary to neuroblastoma or ganglioblastoma. Children with OMS treated with rituximab in addition to the ongoing therapy with ACTH and IVIG showed a 80% clinical improvement, thus proving it to be a safe and efficacious adjunct to the treatment of OMS [24].

*Organ Transplantation*: Rituximab has been used in the setting of solid organ transplantation for prevention of hyperacute rejection, ABO incompatible transplants, treatment of acute and chronic rejection, and treatment of post-transplant lymphoproliferative disorders (PTLD).

PTLD are usually EBV related neoplastic disorders occurring after transplantation, which are treated by reducing the immunosuppression. Severe cases need chemotherapy. Incorporation of rituximab in the treatment of PTLD has led to the decreased use of chemotherapy agents and better outcomes [25].

In a randomized prospective study in the treatment of acute rejection in pediatric renal transplantation, rituximab proved safe and efficacious with recovery of graft function and improvement of biopsy rejection scores at both the 1- and 6-month follow-up biopsies [26]. Chronic antibody mediated rejection in pediatric renal transplant patients has also been successfully treated with a combination of IVIG and rituximab therapy [27].

## DOSE AND ADMINISTRATION

The recommended dose of rituximab in the treatment of lymphoma is 375mg/m$^2$ every weekly for 4-8 weeks or 375mg/m$^2$ given along with the chemotherapy cycle every 2-4 weekly. It is available as 100 and 500 mg vials. The drug dose is diluted in 0.9% saline or 5% dextrose to give a final rituximab concentration of 1-4 mg/mL. Premedication is administered half an hour prior to the infusion with acetaminophen, an antihistaminic like diphenhyramine and a corticosteroid. The infusion is started very slowly at 50 mg/hour for 30 minutes and then increased by 50 mg at every 30 minute intervals.

## ADVERSE EFFECTS

Adverse effects to rituximab can be classified as immediate, acute and delayed.

Immediate reactions are infusion reactions. Their incidence is about 25%, and they could be mild to moderate associated with fever, chills, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, myalgia, and hypertension. Rarely, severe reactions may occur with hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, cardiogenic shock, or anaphylaxis leading to death. Patients with hematolymphoid malignancies are at risk of developing tumour lysis syndrome after treatment with rituximab.

Rituximab causes B cell depletion leading to decreased serum immunoglobulins and lymphopenia. Neutropenia, anemia and thrombocytopenia is seen in less than 5% of the patients. Infectious complications include bacterial infections and reactivation of viral infections. Hepatitis B reactivation can lead to fulminant hepatitis and hepatic failure. Progressive multifocal leucoencephalopathy secondary to reactivation of JC virus has been reported [28].

In February 2007, the US FDA has issued a black box warning on rituximab in view of serious cardiovascular reactions after the first administration of the medication, kidney failure, tumor lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy.

## CONCLUSIONS

Rituximab, the first of the monoclonal antibodies approved has proved to be useful in CD20 positive hematolymphoid malignancies as well as a host of other immune mediated disorders. It is a relatively safe drug. There are several ongoing clinical trials assessing efficacy and safety of rituximab in children with CD20 positive lymphoma, post-transplant lymphoproliferative disease, multiply relapsing

nephrotic syndrome, chronic ITP and SLE. Results of these trials will give validated proof of the role of rituximab in these conditions. Caution needs to be used in planning therapy with this drug that can have significant immune suppression as a side effect.

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