

Rituximab (Anti CD20 Antibody) Based Therapy : A Holy Grail for Both Haematological and Non Haematological Disorders

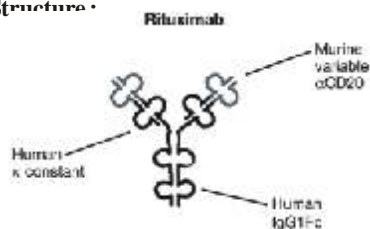
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ABSTRACT

Drug update on Rituximab is like writing and rewriting, the very treatment evolution of haematological malignancies. Besides it is also used in other non-haematological conditions and autoimmune conditions all indications can only be compiled in 2 parts. We have emphasized on haematological malignancies in part I, because rituximab can be compared with the elusive holy grail as far as haematological diseases like DLBCL and CLL are concerned. Part 2 deals with new treatment avenues in non haematological conditions

Class : Monoclonal antibody, Chimerical mouse / human against CD20 antigen.

Structure



Mechanism of action : Not known, May be: Direct signaling, complement dependent cellular cytotoxicity and antibody dependent cellular cytotoxicity all appear to play a role in rituximab efficacy.

Uses :

- Low-grade or follicular CD20-positive non-Hodgkin's lymphoma
- Follicular CD20-positive non-Hodgkin's lymphoma
- Low-grade or follicular CD20-positive non-Hodgkin's lymphoma
- CD20-positive diffuse large B-cell non-Hodgkin's lymphoma
- CD20-positive chronic lymphocytic leukemia, Mantle cell lymphoma.
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)
- Burkitts lymphoma
- Relapsed ALL (CD20+)

- Steroid resistant ITP
- Rheumatoid arthritis
- SLE
- Autoimmune disorders
- Nephrotic syndrome (steroid resistant)
- Steroid resistant ITP
- Solid organ transplantation
- Graves disease
- Multiple sclerosis
- Dermatomyositis and polymyositis
- Pemphigus

Side effects :

1. Infusion reactions
2. Mucositis
3. Hepatitis B reactivation
4. PML (progressive multifocal leucoencephalopathy)
5. Tumour lysis syndrome
6. Late onset neutropenia
7. Reversible progressive leucoencephalopathy
8. Interstitial lung disease

PART I : RITUXIMAB (ANTI CD20 ANTIBODY) : A PANACEA FOR AGGRESSIVE AND INDOLENT HAEMATOLOGICAL MALIGNANCIES

Rituximab (Rituxan; Genentech, Inc, South San Francisco, CA and IDEC Pharmaceutical Corporation, San Diego, CA) is a unique monoclonal antibody for the treatment of non-Hodgkin's lymphoma.

This chimeric mouse/human antibody was discovered in 1991 at IDEC Pharmaceuticals' laboratories, where the antibody was genetically engineered and produced utilizing high-yield expression systems.¹

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Rituximab is the first therapeutic monoclonal antibody approved for the treatment of cancer and the first single agent approved specifically for therapy for a lymphoma. Substantial research has been performed over the past 8 years to further the understanding of this novel therapeutic.²

Mechanism of action : Rituximab targets the CD20 molecule, expressed on normal and malignant B-lymphocytes, the variable murine region of rituximab binds specifically to the CD20 antigen. The intensity of CD20 antigen expression is lower on CLL cells than in patients with NHL and appears to correlate with the level of clinical response. The characteristics that make CD20 a good target antigen include its relatively high level of expression and close location of the extracellular epitopes to the cell surface.³ We know that anti-cancer monoclonal antibodies (mAbs) can mediate anti-tumor effects by a variety of mechanisms like Signaling resulting in cell cycle arrest, Direct induction of apoptosis Sensitization to cytotoxic drugs Complement dependent cytotoxicity (CMC) Antibody dependent cellular cytotoxicity (ADCC).

Role of vitamin D in Rituximab mediated cell cytotoxicity (RMCC) -

Improvement was observed in patients with vitamin D levels more than 8 ng/mL (3-year EFS, 31% v 16%) together with the improvement in RMCC after vitamin D substitution in vivo, holds promise that interventional vitamin D might improve the outcome of vitamin D deficient patients.⁴

Pharmacokinetics (PK) -

Rituximab pharmacokinetics are best described by a two-compartmental model, with mean half-lives of about 1.3 (distribution) and 19 days (elimination).⁵ A receptor binding and saturation mechanism may be involved in the PK process. In addition, higher and more sustained serum levels were achieved after multiple doses than after single doses.⁶ Serum rituximab levels have been shown to be proportional to the antibody dose infused.⁶ The PK of rituximab have been characterized by wide inter-individual variability, with high serum drug concentrations appearing to correlate with the clinical response.⁶

PK parameters of Rituximab were similar to those described for studies in the absence of chemotherapy.⁷ Whether given weekly or monthly, Rituximab is present at therapeutic levels in the circulation of patients for months at a time.⁸

Drug Distribution -

Rituximab is widely distributed to body organs, including heart, liver, lungs, spleen, and kidneys of patients with NHL.⁷ As an IgG, Rituximab distributes in both the intravascular and extravascular compartments, and so should be present within involved lymph nodes with their complex architecture.⁸ The drug is degraded in the liver and other organs by a process of nonspecific catabolism and is mainly excreted renally. 47.5% drug is excreted in the urine⁶ Rituximab injected directly into the cerebrospinal fluid in patients with central nervous system (CNS) lymphoma has been reported to have local anti-lymphoma effects.⁷

Uses -

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5. CD20-positive chronic lymphocytic leukemia, Mantle cell lymphoma.
6. Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)
7. Burkitt's lymphoma
8. Relapsed ALL (CD20+)
9. Steroid resistant ITP.

Rituximab in Follicular lymphoma -

Immunotherapy with Rituximab alone or combined with chemotherapy has demonstrated good results with regard to PFS and, in some instances, Overall Survival. (OS). Single agent rituximab in treatment-naive patients with FL has yielded an overall

response rate (ORR) of 72% to 73%, with a median time to disease progression of just over 2 years. In the relapsed setting, Rituximab has yielded an ORR of 40%, with a median time to disease progression of about 18 months.⁹ In addition to being an effective therapy for FL, rituximab has a low toxicity profile and is tolerated well, even in elderly patients. It also seems to improve the outcomes of certain chemotherapies when added to the regimen.⁹ Several studies proved that rituximab has a better overall survival and median response duration. PRIMA study,¹⁰ and several other studies using maintenance Rituximab in follicular lymphoma supports the use of maintenance Rituximab, with an across-the board improvement in PFS and an improvement in OS in a pooled analysis.¹¹

Rituximab in Diffuse Large B Cell Lymphoma (DLBCL)

Several multicenter clinical trials have documented that the addition of rituximab to a standard CHOP regimen (R-CHOP) increases the efficacy of this first-line treatment, both in older (60 years) and younger DLBCL patients. According to GELA (phase III) trial (Groupe d'Etudes des Lymphomes de l'Adulte) and MInT (Mabthera International Trial), Patients treated with R-CHOP demonstrated a better OS than those from the CHOP arm (median OS not reached after 5 years, vs 3.1 years, P = 0.007).⁷⁰ The CR rates and PFS were also higher in R-CHOP treated patients (76% vs 63% and 3.8 years vs 1.1 years, respectively).

According to RICOVER-60 trial, The R-CHOP-14 program showed advantage over CHOP-14 in regard to PFS and OS. More than six cycles did not improve the Event free survival (EFS). Various studies conducted in this regard have suggested better outcome in the rituximab arm. Rituximab, as already quoted, is used in Mantle cell lymphoma in chronic lymphocytic lymphoma. In CLL rituximab was combined with fludarabine, cladribine, high dose methylprednisolone, mitoxantrone, cyclophosphamide, and importantly with bendamustine. Its role with bendamustine is clinically tolerable and results were encouraging. STILL group has proved noninferiority over R-

CHOP by R-B in mantle and high grade follicular lymphoma.¹²

DRUG UPDATE PART II : RITUXIMAB (ANTI Cd20 ANTIBODY) BASED THERAPY : DISCOVERING NEW TREATMENT HORIZONS IN NON HEAMATOLOGICAL CONDITIONS

Uses -

1. Rheumatoid arthritis
2. SLE
3. Autoimmune disorders
4. Nephrotic syndrome (steroid resistant)
5. Solid organ transplantation
6. Graves disease
7. Multiple sclerosis
8. Dermatomyositis and polymyositis
9. Phephigus

Rituximab (RTX) in Rheumatoid disorder -

Rituximab may have an important place in the treatment of patients with RA who demonstrate an inadequate response to currently available TNF inhibitors. The results of REFLEX and GERINIS also expand the efficacy and safety profile of Rituximab observed in earlier studies of patients with RA in whom previous DMARD therapy had failed. Recently 5 year data of REFLEX trial also confirms the durability of response to rituximab.¹³

In addition, the results demonstrate that RTX monotherapy and in combination with Leflunomide may represent an alternative for some patients intolerant to MTX.¹⁴

ACR guidelines on Rheumatoid arthritis, 2012, also includes use of RTX in low disease and moderately/high disease activity on failure with MTX monotherapy, or with combination with DMARD therapy.¹⁵

Key messages from the current review on SLE -

- B-cell depletion with Rituximab continues to be used in clinical practice for the treatment of refractory SLE, on the basis of a considerable number of publications describing the safety and efficacy data from small open studies and clinical

experience whilst noting that it has not been approved by health authorities for the treatment of lupus.

- A better response to Rituximab detected in patients of African-American and Hispanic ancestry highlights the importance of preplanned subgroup analysis and the need to better understand the potential disease drivers of a treatment effect.
- The significant biological effects seen with Rituximab need to be monitored to assess clinical benefit and risk in the long term.
- Future clinical trial design in SLE and lupus nephritis may be guide¹⁶

Rituximab in other Rheumatoid conditions -

- Rituximab is reported by few anecdotal studies and 1 small RCT to be effective in sjogren syndrome. Systemic manifestations including sicca syndrome responds to rituximab if given early in the disease course infusion reaction and serum sickness to RTX is reported, amenable to steroid and slow infusion.
- In ANCA associated vasculitis, anecdotal reports suggest response with 375 mg/m² of rituximab, except reversal of granulomatous lesion.
- Reduced efficacy and possible persistence of B cell clone have been reported in Mixed cryoglobulinemia¹⁷.

Rituximab in Steroid resistant nephrotic syndrome (SRNS) -

- In Membranous nephropathy (most common cause of nephritic syndrome), B cell activation leads to immunoglobulin deposition along the glomerular basement membrane.
- Few case series and anecdotal reports suggests use of Rituximab in steroid refractory membranous nephropathy.
- Response is usually late, upto 12 months later.
- No consensus on dosing, both 375 mg/m² for 4 weeks and 1000 mg twice have been used.
- Peak level of rituximab is lower in SRNS.¹⁷

Rituximab in ITP-

- The response (platelet count >50×10⁹/L) and complete response (platelet count >150×10⁹/L) rate in children and adults with primary ITP obtained is around 64% and 40% respectively
- The frequently administrated dose of rituximab is 375 mg/m² per week for 4 weeks for both children and adult with ITP.
- Treatment of rituximab is still costly, Low dose of rituximab may be promising for patients with ITP, and more studies are needed to investigate that.
- Adverse effects were mild to moderate infusional reaction only.
- More severe adverse effects included serum sickness, common variable immunodeficiency, severe virus infection including enteroviral meningoencephalitis, and white matter changes.
- Studies on this topic with better methodological design like randomized controlled studies are urgently needed.¹⁸

Renal transplant : Rituximab plays a pivotal role in renal transplantation, it is being studied for its benefits in ABO incompatible transplants, preformed antibody mediated graft rejection and to prevent acute rejection.¹⁷

Cardiac and liver transplantation : Anecdotal reports are suggestive of role of rituximab in reducing humoral rejection in cardiac transplantation and antibody mediated rejection in liver transplantation¹⁷.

Multiple sclerosis : Phase I and II studies have shown rituximab to be an effective single agent treatment in relapsing remitting MS.¹⁷

Myasthenia gravis : especially with MuSK antibody and to lesser extent AChR antibody, responds to rituximab 375mg/m² weekly for 4 weeks.

Graves disease : Addition of rituximab 375mg/m², to antithyroid drug, increases the long term remission rates in graves disease. Reduction of the stimulatory capacity of thyroid stimulating receptor (TRAb) have been postulated.¹⁷ Rituximab is as

effective as steroids in improving eye disease however, after 12 months follow up, the relapse rate is reduced in patients treated with rituximab compared to those treated with steroids (0% vs. 10%)¹⁹. Rituximab has also been reported to be effective in patients who have been refractory to steroids.²⁰

Pemphigus : Two prospective open label studies achieved over 80% complete remission. Response can be seen from about 4 weeks after treatment, with mucosal lesions taking longer to respond than skin lesions. Between 44% and 100% of patients were able to discontinue all other immunosuppressive medication with follow up between two and a half and three years.¹⁷

Adverse effects -

1. 10% of patients have shown a severe infusion-related reaction which may be accompanied by fever, bronchospasm, hypotension, and angioedema. Infusion-related adverse effects occur within the first 30 minutes to 2 hours of starting the first infusion, and are usually reversible with interruption or discontinuation of rituximab along with supportive care.
2. Higher risk of developing hypogammaglobulinemia, and 10% required intravenous immune globulin infusion for infection.
3. Recent data indicates that rituximab increases the risk of hepatitis B virus reactivation (HBV in patients with resolved infection).
4. Other viruses have also been reported in association with rituximab-containing regimens. Severe herpes virus reactivation including cytomegalovirus and varicella zoster has been reported in several patients.
5. Some reports have indicated that Parvovirus B19 with pure red cell aplasia¹⁵ and West Nile virus may be linked to treatment with rituximab.
6. Progressive multifocal leukoencephalopathy (PML) a lethal, progressive demyelinating disorder of the central nervous system (CNS) characterized by the destruction of

oligodendrocytes due to the reactivation of the John Cunningham (JC) virus (a type of human polyoma virus).

7. Addition of rituximab to standard chemotherapy increases the risk of severe leukopenia and granulocytopenia.
8. Rituximab induced interstitial lung disease is a rare but known side effect.

FDA approval -

- **Non-Hodgkin's Lymphoma (NHL) :** alone or with other chemotherapy medicines
- **Chronic Lymphocytic Leukemia (CLL) :** with the chemotherapy medicines fludarabine and cyclophosphamide
- **Rheumatoid Arthritis (RA) :** with another prescription medicine called methotrexate, to reduce the signs and symptoms of moderate to severe active RA in adults, after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well enough.
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis)
- **Microscopic Polyangiitis (MPA) :** with glucocorticoids, to treat GPA and MPA.²¹

Conclusions -

Currently, this drug is commonly combined with firstline chemotherapy for Follicular Lymphoma. PRIMA study showed that rituximab maintenance doubled the PFS of patients with FL compared to those who stopped treatment. Randomized Phase III trials have demonstrated the superiority of R-CHOP over CHOP chemotherapy alone in patients with DLBCL Future studies will combine Rituximab with emergent targeted drugs such as flavopiridol, lenalidomide, and orally bioavailable tyrosine kinase inhibitors.

Rituximab therapy is discovering new horizons, it is reported not only to be useful in the B cell mediated disease conditions, but also in the T cell mediated diseases. Explaining the interrelation between B-T mediated diseases. Reports of the use of rituximab

are largely anecdotal and results are mostly biased. This underscores the need for randomized control trial (RCT), to prove the role of rituximab in various non hematological conditions. Besides side effect profile is also variable in different conditions. The dose schedule of rituximab and its infusional rate needs to be verified by RCT.

References :

1. Pescovitz, M. D. Rituximab, an Anti-CD20 Monoclonal Antibody : History and Mechanism of Action. *American Journal of Transplantation*,(2006) 6: 859866. doi : 10.1111/j.1600-6143.2006.01288.
2. Grillo-López AJ . Rituximab: an insider's historical perspective. *Seminars in Oncology* [2000, 27(6 Suppl 12):9-16] PMID:11226006.
3. Beers SA, Chan CH, French RR, Cragg MS, Glennie MJ. CD20 as a target for therapeutic type I and II monoclonal antibodies. *Semin Hematol.* 2010;47(2):107114.
4. Bittenbring JT, Neumann F, Altmann B, Achenbach M, Reichrath J, Ziepert M et al. Vitamin d deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. *J Clin Oncol.* 2014 Oct 10;32(29):3242-8. doi: 10.1200/JCO.2013.53.4537. Epub 2014 Aug 18.
5. Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cel.lymphoma. *Drugs.* 2010;70(11):14451476.
6. Robak T, Robak P, Smolewski P: The evaluation and optimal use of rituximab in lymphoid malignancies. *Blood Lym Can Targets Ther.* 2012,2:116.
7. Blasco, H., Chatelut, E., De Bretagne, I. B., Congy-Jolivet, N. and Le Guellec, C. (2009), Pharmacokinetics of rituximab associated with CHOP chemotherapy in B-cell non-Hodgkin lymphoma. *Fundamental & Clinical Pharmacology*, 23: 601608. doi: 10.1111/j.1472-8206.2009.00714.x.
8. George J. Weiner. Rituximab: Mechanism of Action. *Seminars in Hematology*, Vol 47, No 2, April 2010, pp 115123.
9. Bello C, Zhang L, Naghashpour M. Follicular lymphoma: Current management and future directions. *Cancer Control.* 2012 Jul;19(3):187-95.
10. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet.* 2011;377(9759):42-51.
11. Vidal L, Gafter-Gvili A, Leibovici L, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst.* 2009;101(4):248-255.
12. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C et al. Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet.* 2013 Apr 6;381(9873):1203-10. doi: 10.1016/S0140-6736(12)61763-2. Epub 2013 Feb 20.
13. Keystone EC, Cohen SB, Emery P, Kremer JM, Dougados M, Loveless JE, et al. Multiple courses of rituximab produce sustained clinical and radiographic efficacy and safety in patients with rheumatoid arthritis and an inadequate response to 1 or more tumor necrosis factor inhibitors: 5-year data from the REFLEX study. *J Rheumatol.* 2012 Dec;39(12):2238-46. doi: 10.3899/jrheum.120573. Epub 2012 Oct 1.
14. Wendler J, Burmester GR, Sörensen H, Krause A, Richter C, Tony HP, et al. Rituximab in patients with rheumatoid arthritis in routine practice (GERINIS): six-year results from a prospective, multicentre, non-interventional study in 2,484 patients. *Arthritis Res Ther.* 2014 Mar 26;16(2):R80. doi: 10.1186/ar4521.
15. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012 May;64(5):625-39. doi: 10.1002/acr.21641.
16. Reddy V, Jayne D, Close D, Isenberg D. B-cell depletion in SLE: clinical and trial experience with rituximab and ocrelizumab and implications for study design. *Arthritis Res Ther.* 2013;15 Suppl 1:S2. doi: 10.1186/ar3910. Epub 2013 Feb 11.
17. McDonald, V. and Leandro, M. Rituximab in non-haematological disorders of adults and its mode of action. *British Journal of Haematology*, 2009, 146: 233246. doi: 10.1111/j.1365-2141.2009.07718.x

18. Liang Y, Zhang L, Gao J, Hu D, Ai Y (2012) Rituximab for Children with Immune Thrombocytopenia: A Systematic review. PLoS ONE 7(5): e36698. Doi:10.1371/journal.pone.0036698.
19. Salvi, M., Vannucchi, G., Campi, I., Curro, N., Dazzi, D., Simonetta, S., et al Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. European Journal of Endocrinology, 2007; 156, 3340.
20. El Fassi, D., Nielsen, C.H., Hasselbalch, H.C. & Hegedus, L. Treatment-resistant severe, active Graves' ophthalmopathy successfully treated with B lymphocyte depletion. Thyroid, 2006; 16, 709710.
21. Rituximab (marketed as Rituxan) Information. www.fda.gov/Drugs/DrugSafety/.../ucm109106.htm