Massachusetts Institute of Technology

Rituximab: Prospects for treatment of Multiple Sclerosis

MIT Student

Introduction

Rituximab (Ritxuan; RTX), one of the worlds top selling biologics, is a chimeric monoclonal antibody that selectively targets B-cell lymphocytes (B-cells) for destruction. RTX is currently approved by the FDA for the treatment of Non-Hodgkin's Lymphoma (NHL), chronic lymphocyte leukemia (CLL), rheumatoid arthritis (RA), and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).[1] Although originally developed to treat diseases associated with cancerous B-cells, recent clinical trials have shown that RTX is effective in the treatment of autoimmune diseases such as multiple sclerosis (MS), revealing a novel role of B-cells in disease pathophysiology. Given the limited treatments available for MS, the use of RTX to reduce adverse events and brain lesions may represent a more long-term and safe therapy. RTX's patent is set to expire in 2015, thus, the potential for developing biosimilars and the development of new anti-CD20 therapies create an uncertain future for Phase III clinical trials. The effectiveness and proven safety record of RTX indicate a need to further develop this therapy for MS, however, trials have been halted in favor of another CD20 therapy, Ocrelizumab (OCR), that has proven efficacious but unsafe in Phase I/II and III trials. Thus, it could be argued that commercial interests, rather than patient interests, have prevailed in the case of RTX.

Mechanism of Action, Pharmacokinetics and Pharmacodynamics

Rituxumab (RTX), shown in Figure 1A, was developed by IDEC Pharmaceuticals and was originally approved to treat NHL in 1997.[2] The 2009 worldwide sales of RTX, one of the top three selling biopharmaceuticals, were \$5.6 billion.[3] The cost-per life gained of RTX has been estimated to be between \$50,000 to \$100,000.[4] RTX is administered as an IV drip over the course of 2-4 hours, and a single course of treatment usually consists of two 1000 mg doses given two weeks apart, however, the dose and dosing regime can vary for each indication.[1] Side effects usually appear within the 24 hours after infusion, and can include a blood pressure drop, flu-like symptoms such as rash, itchiness, dizziness and back pain, cardiac arrest, cytokine release syndrome, tumor lysis syndrome due to massive B-cell death (causing acute renal failure), and viral infections.[5] Rare severe side effects include the development of progressive multifocal leukoencephalopathy (PML), severe skin reactions and mouth sores (FDA). PML is a demyelinating disease caused by the reactivation of the normally dormant JC virus (JCV), which spreads to the brain.[5,6] The destruction of B-cells leaves patients susceptible to bacterial and viral infections, and overall about 5.3% of patients report serious infections when taking RTX.[7] RTX is commonly used in conjunction with chemotherapy to treat cancers.[5]

RTX is a monoclonal chimeric antibody containing human IgG_1 and $\varkappa$ chain constant regions with murine variable regions that recognize its target, CD20.[8] RTX binds to the transmembrane phosphoprotein CD20, shown in Figure 1B, a receptor that is highly B-cell specific and expressed on pre and mature B-cells, does not internalize or shed, and is not down-regulated.[5,9] CD20 is not expressed on hematopoietic stem cells, pro-B-cells, normal plasma cells, or on other tissues, thus the off target effects of RTX are low.[5] The role of CD20 is unknown but it is believed to play a role in Ca^{2+} influx to allow for activation of B-cells.[9] As shown in Figure 2A, RTX eliminates B-cells through activating both the antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (CDC) pathways of the immune system, and by inducing programmed cell death (PCD).[10] B-cells can be directly destroyed by a variety of effector cells, including natural killer cells and macrophages.[11] Thus, RTX is used to treat diseases characterized by over-active, over-proliferative, or dysfunctional B-cells, such as leukemia and lymphoma. It is further hypothesized that RTX induces B-cell death by effecting the cell cycle, increasing MHC II and adhesion molecules, eliciting shedding of

CD23, down-regulating the B-cell receptor, and ultimately inducing apoptosis.[10,12,13] The current understanding of the mechanism of action of RTX is that all of these processes are not mutually exclusive, and likely act in concert to destroy both healthy and cancerous B-cells. The incredibly potent and selective depletion of B-cells poises RTX to be a therapeutic that is capable of mitigating many diseases that involve pathogenic or dysfunctional B-cells.

The pharmacokinetics and pharmacodynamics (PK/PD) of RTX is similar to other IgGs, and whether given monthly or weekly RTX is present at therapeutic levels in the circulation for months.[5,13,14] The IV route of administration allows for high and rapid systemic availability, but also increases the cost of treatment.[13] It has been shown that post injection, RTX distributes to the intravascular and extravascular compartments leading to a low volume of distribution (V_d) and high bioavailability, and thus, is present in the lymph nodes where it can target developing B-cells.[11,14] The rapid clearance of B-cells is shown in Figure 3B, where B-cells are depleted over the course of a 4 hour infusion. As shown in Figure 3A, mouse PK/PD studies indicate that tumor burden can significantly affect serum RTX concentrations, exposure, and response to treatment.[15] This may partially account for clinical heterogeneity of RTX treatment. PK/PD data from clinical trials is summarized in Table 1. The half-life of RTX is on the order of days, leading to the sustained decrease in $CD19^+$ B cells for weeks to months. No formal studies have examined the effects of renal or hepatic impairment on the PK of RTX.[5] As shown in Figure 2B, the primary determinants of distribution and elimination include rates of diffusive transport into tissue and return by lymphatic circulation, active transport mediated by the FcRn receptor, and catabolism. The receptor associated with IgG transport and recycle, FcRn, is expressed in a wide variety of tissues, including the endothelial cells of the liver, kidneys, lungs, and hapatocytes.[13] It is believed that this receptor plays a key role in the movement and distribution of IgG, where IgG is transported between the peripheral blood, tissues, and recycled through the lymphatic system.[13] The kidney or liver filters little intact IgG, due to its size. The majority of IgG is cleared by catabolism and break down by proteases, however, IgG are very stable *in vivo*.

RTX is not effective for all patients, and development of resistance to therapy has been reported. As shown in Figure 6, heterogeneous responses can be seen with Rituximab, where overall 13.3% of patients show no response, 45.1% show partial response, and 41.6% show a complete response.[7] This may be due to the expression of other CD markers on B-cells, such as CD55 and CD59, which can interfere with CDC in lymphoma cell lines.[9] Polymorphisms in CD16 have been correlated to clinical outcome in RTX treatment of follicular lymphoma, where CD16 homozygotes for a mutation to valine (VV) have a better clinical response.[12] Furthermore, it is believed that the mechanism of action of anti-CD20 antibodies can very depending on the epitope targeted. Studies that have aimed to determine the mechanism of action of RTX fail to do so in the context of effector cells, like NKs, thus they fail to show how these cells may interact to cause B-cell death. Formal drug interaction studies have not been performed with RTX, however, in clinical trials it was observed that RTX did not alter the exposure to fludarabine or cylclophosphamide and in patients with RA RTX pharmacokinetics were not altered when given with methotrexate or clycophosphamide.[1] Safety for pediatric patients has not been tested due to the worry that depleting B-cells in a developing immune system could lead to immunosuppression.[5]

Next-generation B-cell depleting monoclonal antibodies (mAbs), as shown in Table 2, include ocrelizumab (OCR), ofatumumab, and third generation mAbs with engineered Fc regions to increase ADCC and CDC by the immune system. These agents have been tailored to enhance therapeutic efficacy through altering the balance of the various proposed mechanisms of action. For example, OCR targets the same epitope as RTX, but in order to minimize immunogenicity it

is a fully humanized mAb. Ofatumumab is a fully humanized mAb, however, its epitope is different than RTX. As compared to RTX, it exhibits CDC activity in RTX resistant cell lines, has a lower dissociation constant, and induces less PCD.[10] The epitope specificity, engineered Fc region, production and purification, and chimeric status of each mAb alter their therapeutic functionality. It is unclear how these modifications link to clinical outcome, however, next generation anti-CD20 may provide alternative treatments for patients that are resistant to RTX. Due to its potent and specific mechanism of action, favorable PK/PD, and large therapeutic index (375 to 1000 mg/infusion), RTX has the potential to treat many diseases in which B-cells contribute to disease pathophysiology.

Ocreluzimab, Rituximab, and Multiple Sclerosis

Successful treatment of autoimmune diseases with B-cell depleting agents, like RTX, has provided novel insight into the mechanisms by which B-cells contribute to disease. Multiple sclerosis (MS) is an autoimmune disease characterized by the demyelination of the central nervous system (CNS), leading to progressively debilitating physical and mental neurological symptoms. Demyelination is caused by myelin-specific T-cells that target myelin antigens, leading to a strong inflammatory response in the CNS and destruction of myelin-producing oligodentrocyte cells.[16] Due to the difficulties associated with accessing the CNS because of the blood-brain barrier (BBB) and limited knowledge of MS pathogenesis, treatments are currently limited. Disease-modifying treatments include the cytokines interferon β -1a and 1b, mitoxantrone (immunosuppressant), natalizumab, and teriflunomide. Many of these drugs, such as interferon β 1a and 1b, can have serious side effects that lower the quality of life for MS patients.[17] MS usually begins as a relapsing, episodic disorder (relapsing-remitting MS; RRMS), and then evolves into a chronic neurodegenerative condition characterized by progressive neurologic disability (PPMS).[16,18] As shown in Figure 4, MS has traditionally been viewed as a T-cell-mediated disease.[19,20] Auto-reactive T-cells extravasate into the CNS, resulting in a cascade of inflammatory events that leads to CNS lesions and weakening of the BBB. Gadolinium-enhanced lesions (GELs) are detected by magnetic resonance imaging, thus, are crucial end points of MS clinical trials.[18,19]

Successful treatment of MS with RTX has revealed a novel role for B-cells in the pathophysiology of MS, and there are currently 37 open antibody therapy trials for MS treatment (Figure 5). In a Phase II clinical trial with RTX in patients with RRMS, it was found that patients who received RTX showed reduced GEL counts in the CNS, a reduction in the number of relapses (P=0.04, week 48), and a decrease in infusion reaction related events over the 48 week timespan of the study.[18,21] A single course of RTX reduced GELs as compared to baseline and reduced clinical relapse, however, a longer time course is needed as part of Phase III clinical trials.[18] In contrast to this, a phase II/III study determined that RTX had no significant clinical impact for PPMS.[22] Compared to placebo, time to confirmed disease progression (CDP) was delayed in RTX treated patients aged <51 (p = 0.010) and the incidence of adverse events was comparable among all groups.[22] This suggests that the rate of disease progression may be a crucial factor in predicting outcomes of B-cell therapies in MS. B-cells contribute to developing autoimmunity by producing autoantibodies directed against self-antigens, as is the case in MS. These autoantibodies can complex with self-antigens, leading to immune system activation, local inflammation, and the subsequent pathology.[6] RTX does not deplete long-lived plasma cells, thus revealing a pathogenic role for non-antibody secreting B-cells.[11] These B-cells may act as antigen presenting cells or perform other functions to stimulate auto-reactive T cells. The results for PPMS treatment, coupled with the diverse functions of non-secreting B-cells, could indicate

that the degree to which B-cells contribute to disease pathology changes over time, perhaps in concert with the patient's immune system.

OCR is a fully humanized version of RTX that binds to an overlapping epitope of CD20 and was characterized *in vitro* to have enhanced ADCC and reduced CDC activities as compared to RTX.[10,23] OCR was developed with the goal of decreasing immunogenicity due to its humanized form and to decrease side effects by the reduction in CDC activity through a glyco-engineered Fc region. In a phase I/II clinical trial, participants with RA were given increasing doses of OCR up to 1000 mg per infusion and monitored for 72 weeks.[23] The goal of this study was to determine if OCR was safe and efficacious in combination with methotrexate, a first-line RA therapy. It was found that B-cells were rapidly depleted in a dose dependent manner, however, the authors failed to present safety data comparing OCR to RTX, to identify subsets of patients whose need was currently un-met by RTX, or to show an improved risk-benefit profile as compared to RTX. In a follow-up phase III trial, a high rate of serious infections were reported, leading to three deaths of patients receiving 500 mg of OCR.[24,25] Furthermore, the overall response rates were comparable to RTX, highlighting the similar effectiveness between the two therapies, showing that there really is not a clear need to develop OCR for RA therapy.[7,24] Hoffmann-La Roche discontinued its pursuit of OCR as an RA therapy shortly after.[26]

Despite clear safety concerns with OCR, as shown in Table 3, there are currently three open clinical trials for the treatment of MS with OCR sponsored by Hoffmann-La Roche. In a phase II trial with OCR for treatment of RRMS, Kappos *et al*. showed that the number of new GELs was lower in the OCR group (p<0.0001). However, one death was reported for the OCR group, and treatment with OCR cannot be excluded.[25,27] The expected patent expiration of RTX and the burgeoning development of RTX biosimilars could explain the reluctance of Roche to pursue phase III trials with RTX. It is clear that commercial interests in developing OCR are taking precedence, which could compromise patient safety and hinder the development of RTX as a verified on-label MS treatment. This condemns RTX to remain an off-label last-line treatment for patients with MS despite its proven efficacy in clinical trials and its long-term safety profile since its development in 1997.

Future Prospects: Next Generation CD20s and Biosimilars

Biosimilars, or follow-on biologics, are active drugs produced by a living organism or derived from a living organism. With 8 of the top 10 selling biologics coming off patent in 2015, the market for biosimilars is expected to increase by 700% between 2010 and 2015.[28] The development of RTX biosimilars, potentially for MS indications, may play a role in treatment given that the pursuit of RTX phase III trials has been halted. Competitive biosimilars could save MS patients thousands of dollars per year, however, the challenges associated with the development of biosimilars could delay their market entry in the US.[29] The complex molecular nature and production of biosimilars, coupled with evolving FDA regulations on approval, create an uncertain future for several important biologics such as RTX. Furthermore, inherent to the nature of biosimilars is the potential for creating immunogenicity with small changes in structure or even in the production cell line.[28] The abbreviated PK-PD studies that were suitable for proving equality as part the Hatch-Waxman Act for small molecule generics is not suitable for biosimilars.[28,30] The FDA recently released its draft guidance regarding the Biologics Price Competition and Innovation (BCPI) Act of 2009 for biosimilars.[31-33] In essence, the data required for biosimilarity will be judged on a case-by-case basis and in order to mitigate immunogenicity, clinical data may be required. The complexity of biologics, coupled with an incomplete

understanding of their *in vivo* mechanisms, creates a unique and complex manufacturing environment as well.

Through the lens of the RTX/OCR story, there are several key factors that could impact future development of RTX for MS. The more intense regulatory environment for biosimilars may act as an incentive to create new biologics rather than biosimilars since expensive clinical data may be required in both cases, but for a new biologic the exclusivity and patent rights are available. Additionally, it could be argued that the development of OCR was justified as a smarter business alternative given the looming development of RTX biosimilars. Counter to this, it could be argued that given the time and expense associated with the development of biosimilars, if Hoffmann-La Roche decided to follow through with RTX treatment of MS, they may enjoy a substantial monopoly on RTX for that particular indication. This can be explained by the data exclusivity policy, which was designed to preserve innovation. This could be a major obstacle for companies looking to develop biosimilars since data about manufacturing can be key to biologic sucess, thus, leading to lengthier clinical and manufacturing verifications. This could lead to larger market shares for their parent drugs during that time. A number of companies, like Novartis, Celltrion, and Samsung are developing biosimilar versions of RTX, and Sweden-based Boehringer Ingelheim is planning to finish clinical studies in 2015.[34] To counter these, Roche has developed several novel anti-CD20 agents, and one (GA101) performed substantially better than RTX in clinical trials for NHL.[35] The development of novel anti-CD20s, especially given the hypothesis that different epitopes may lead to various functional clinical outcomes, could lead to better treatments in the long-run if immunogenicity is mitigated properly. Disappointingly, it is clear that for now further development of RTX for the treatment of MS is unlikely. The emergence of biosimilars may provide MS patients with a more cost effective off-label treatment, but it is unclear if these biosimilars will truly be therapeutically equivalent.

Conclusion

RTX may represent a crucial facet of MS treatment with minimal side effects and has also revealed a novel role for B-cells in disease pathology. Given the results for RTX treatment of PPMS and RRMS, it is clear that the following are needed in order to appreciate the full benefit of B-cell depleting therapy for MS: (1) A mechanistic understanding of B-cells in the context of MS and whether patients can benefit from intrathecal delivery of CD20 agents.[36] Congruent to this, an overall understanding of the role of CNS resident and peripheral B-cells in disease pathology is needed. (2) Functional link between how epitope and Fc composition translates to efficacy and side effects *in vivo*. This may be determined through animal models, like those used by Dayde *et al*., with a series of modified CD20 IgGs. (3) A better understanding of how selective depletion of long-lived plasma B-cells may affect disease state over time since autoantibodies are still found in RTX patients.[21] The development of novel anti-CD20's and the looming production of RTX biosimilars may have influenced the decision to disband RTX phase III clinical trials in favor of OCR, despite issues with safety. The effectiveness and proven safety record of RTX indicate a need to further develop this therapy for MS, however, patient interests may have been trumped by commercial interests and clinical trials with other anti-CD20 agents such as OCR for MS treatment are likely to be pursued.

References

1. CDER, F. Rituxan (rituximab) Label. 1–40 (2012).
2. Maloney1997. 1–8 (1997).
3. GaBi Sandoz announces biosimilar rituximab. *Generics and Biosimilars Initiative* 1–2 (2012).
4. Farber, C. M. & Axelrod, R. C. The clinical and economic value of Rituximab for the treatment of hematologic malignancies. *Contemporary Oncology* 1–17 (2012).
5. CDER, F. Rituxan (rituximab) Label. 1–40 (2012).
6. Engel, P., Gomez-Puerta, J. A., Ramos-Casals, M., Lozano, F. & Bosch, X. Therapeutic Targeting of B Cells for Rheumatic Autoimmune Diseases. *Pharmacological Reviews* **63**, 127–156 (2011).
7. Tony, H.-P. *et al*. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). *Arthritis Research & Therapy* **13**, R75 (2011).
8. Du_2007. 1–8 (2007).
9. Binder, M. The epitope recognized by rituximab. *Blood* **108**, 1975–1978 (2006).
10. Oflazoglu, E. & Audoly, L. Evolution of anti-CD20 monoclonal antibody therapeutics in oncology. *mAbs* **2**, 1–6 (2010).
11. Weiner, G. J. Rituximab: Mechanism of Action. *Seminars in Hematology* **47**, 115–123 (2010).
12. Weiner, G. J. Rituximab: Mechanism of Action. *Seminars in Hematology* **47**, 115–123 (2010).
13. Lobo, E. D., Hansen, R. J. & Balthasar, J. P. Antibody pharmacokinetics and pharmacodynamics. *J. Pharm. Sci*. **93**, 2645–2668 (2004).
14. Blasco, H., Chatelut, E., de Bretagne, I. B., Congy-Jolivet, N. & Le Guellec, C. Pharmacokinetics of rituximab associated with CHOP chemotherapy in B-cell non-Hodgkin lymphoma. *Fundamental & Clinical Pharmacology* **23**, 601–608 (2009).
15. Dayde, D. *et al*. Tumor burden influences exposure and response to rituximab: pharmacokinetic-pharmacodynamic modeling using a syngeneic bioluminescent murine model expressing human CD20. *Blood* **113**, 3765–3772 (2009).
16. Fletcher, J. M., Lalor, S. J., Sweeney, C. M., Tubridy, N. & Mills, K. H. G. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. *Clinical & Experimental Immunology* **162**, 1–11 (2010).
17. NMSS The MS Disease-Modifying Medications. *National Multiple Sclerosis Society* 1–14 (2012).
18. Hauser, S. *et al*. B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis. *New England Journal of Medicine* **3358**, 676–688 (2008).
19. Hartung, H.-P. & Kieseier, B. Antacicept: targeting B cells in multiple sclerosis. *Therapeutic Advances in Neurological Disorders* 1–12 (2010).
20. Miller, S. D., Turley, D. M. & Podojil, J. R. Antigen-specific tolerance strategies for the prevention and treatment of autoimmune disease. *Nature Publishing Group* **7**, 665–677 (2007).
21. Smith, C. H., Waubant, E. & Langer-Gould, A. Absence of Neuromyelitis Optica IgG Antibody in an Active Relapsing-Remitting Multiple Sclerosis Population. *J Neuro-Opthalmol* **29**, 1–3 (2009).
22. Hawker, K. *et al*. Rituximab in patients with primary progressive multiple sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. *Ann Neurol*. **66**, 460–471 (2009).
23. Genovese, M. C. *et al*. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I/II randomized, blinded, placebo-controlled, dose-ranging study. *Arthritis Rheum* **58**, 2652–2661 (2008).
24. Rigby, W. *et al*. Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a forty-eight-week randomized, double-blind, placebo-controlled, parallel-group phase III trial. *Arthritis Rheum* **64**, 350–359 (2012).
25. MD, P. L. K. *et al*. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *The Lancet* **378**, 1779–1787 (2011).
26. Reid, K. UPDATE 4-Roche, Biogen suspends arthritis drug after deaths. *Thomson Reuters* 1–1

(2012).

27.   Chaudhuri, A. Ocrelizumab in multiple sclerosis: risks and benefits. *The Lancet* **379**, 1196–1197 (2012).

28.   Liang, B. & Timothy, M. Biosimilars and patient safety risk: promoting policy protections in the health delivery system. *Reviews in Health Care* **3**, 71–74 (2012).

29.   Geschek, P. Rituxan And Its Biosimilar Competitors. *Seeking Alpha* 1–3 (2012).

30.   Krishnaiah, Y. S. R. Bioequivalence of Follow-on Biologics or Biosimilars. *J Bioequiv Availab* **01**, i–ii (2009).

31.   OMALLEYS, F. C. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. 1–18 (2012).

32.   OMALLEYS, F. C. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product. 1–20 (2012).

33.   OMALLEYS, F. C. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 1–25 (2012).

34.   FirstWord Rituxan biosimilars reach late-stage development, although regulatory concerns remain. *wwwfirstwordcom* 1–2 (2012).

35.   Roche First head to head study shows higher response rates for GA101 vs. MabThera/Rituxan without appreciable differences in safety in common type of blood cancer. *www.roche.com* 1–3 (2012).

36.   Rubenstein, J. L. *et al*. Phase I Study of Intraventricular Administration of Rituximab in Patients With Recurrent CNS and Intraocular Lymphoma. *Journal of Clinical Oncology* **25**, 1350–1356 (2007).

Table 1: Reported Pharmacodynamics and Pharmacokinetics of RTX *in vivo* (Source: FDA)

Disease	Pharmacodynamics	Pharmacokinetics
Non-Hodgkins Lymphoma (NHL)	Depleted CD19$^+$ B cells within first 3 weeks, sustained depletion for 6 to 9 months. B-cell levels returned to normal after 1 year.	Dose: 375 mg/m^2, for four doses. RTX detectable in serum for 3 to 6 months after final dose. $t_{1/2} \sim 22$ days
Rheumatoid Arthritis (RA)	Depleted CD19$^+$ B-cells within 2 weeks, sustained depletion for 6 months. 4% of patients showed B-cell depletion for 3 years.	C_{max1} and C_{max2}: 157 and 183 mcg/mL for two 500 mg doses. Clearance: 0.335 L/day $V_d = 3.1L$ $t_{1/2} \sim 18$ days.
Wegener's Granulomatosis and Microscopic Polyangiitis	Depleted CD19$^+$ B-cells following two infusions of RTX. Remained low for 6 months in 84% of patients. By month 12, 81% of patients showed B-cell return.	Dose: 375 mg/m^2 $t_{1/2} \sim 23$ days Clearane: 0.312L/day $V_d = 4.5L$

Table 2: Characteristics and Indications of example next-generation CD20 mAbs. (Source: Oflazoglu *et al*. 2010)

mAb	Format	Indication	Manufacturer	Binding Site	Phase
Rituximab	cIgG1	NHL, RA	Genentech, Biogen	Type I	Approved (1997)
Reditux	cIgG1 (biosimilar)	NHL	Dr. Reddy Labs	Same as RTX	Approved (2007, India)
Zevalin	mIgG1	NHL	Biogen IDEC	Same as RTX	Approved (2002)
Ofatumumab	hIgG1	CLL,NHL, RA	Genmab, GlaxoSmithKline	Different than RTX	Approved (2009)
Ocrelizumab	hIgG1	NHL, RA	Genentech, Roche, Biogen	Same as RTX	Phase 3
Veltuzumab	hIgG1	NHL, ITP	Immunomedics	Same as RTX	Phase 2

Table 3: Summary of clinical trials with Ocrelizumab (4), Ofatumumab (1), and Rituximab (4) for MS treatment. Total of 950 studies listed for MS treatment alone. (Source: www.clinicaltrials.gov)

mAb	Trial ID	Trial Title	Sponsor	Result
Rituximab	NCT01212094	Double Blind Combination of Rituximab by Intravenous and Intrathecal Injection Versus Placebo in Patients With Low-Inflammatory Secondary Progressive Multiple Sclerosis (RIVITaLISe)	National Institute of Neurological Disorders and Stroke (NINDS)	Recruiting
Rituximab	NCT01569451	Comparison of Rituximab Induction Therapy Followed by Glatiramer Acetate Therapy to Glatiramer Acetate Monotherapy for MS (GATEWAY II)	University of Colorado, Denver	Recruiting
Rituximab	NCT00097188	A study to evaluate rituximab in adults with relapsing remitting multiple	Genentech	Completed Hauser *et al*.

		sclerosis		2008 Smith *et al*. 2009
Rituximab	NCT00087529	A Study to Evaluate the Safety and Efficacy of Rituximab in Adults With Primary Progressive Multiple Sclerosis (OLYMPUS)	Genentech	Completed Hawker *et al*. 2009
Ofatumumab	NCT01457924	Ofatumumab Subcutaneous Administration in Subjects With Relapsing-Remitting Multiple Sclerosis (MIRROR)	GlaxoSmithKline	Recruiting
Ocrelizumab	NCT01247324	A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Patients With Relapsing Multiple Sclerosis	Hoffmann-La Roche	Recruiting
Ocrelizumab	NCT01412333	A Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Patients With Relapsing Multiple Sclerosis	Hoffmann-La Roche	Recruiting
Ocrelizumab	NCT01194570	A Study of Ocrelizumab in Patients With Primary Progressive Multiple Sclerosis	Hoffmann-La Roche	Recruiting
Ocrelizumab	NCT00676715	A Study of the Efficacy and Safety of Ocrelizumab in Patients With Relapsing-Remitting Multiple Sclerosis	Genentech	Ongoing
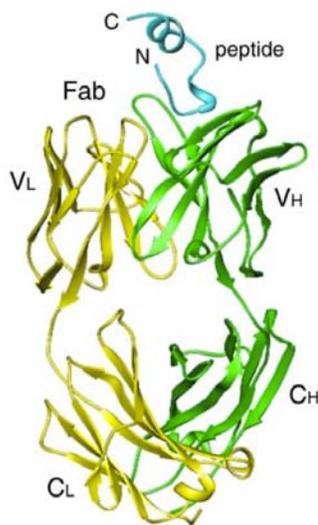
A.
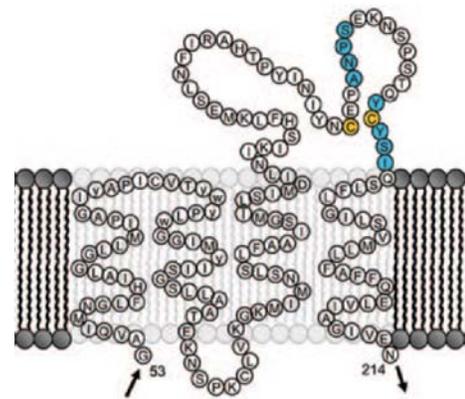
B.

Figure 1. **A.** Crystal structure of Rituximab in complex with its molecular target, CD20, where the proposed epitope is highlighted in blue (Source: Du *et al*. 2007). **B.** Molecular target of Rituximab, CD20, showing the transmembrane and extracellular domain with discontinuous epitopes highlighted in blue. The disulfide bridge between C^{167} and C^{183} is shown in yellow (Source: Binder *et al*. 2006).
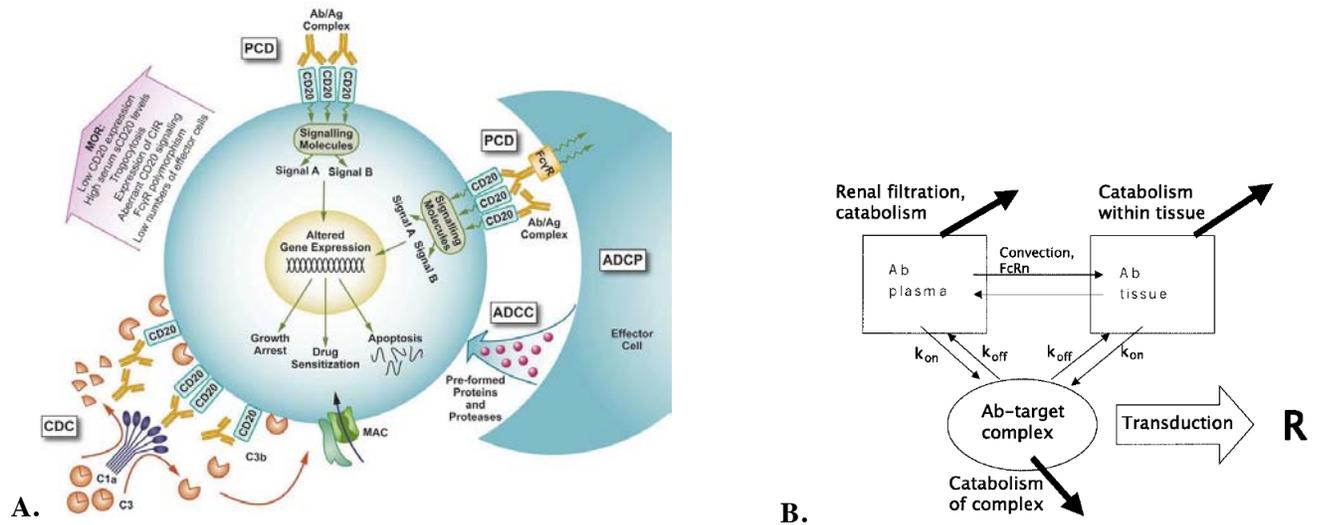
Figure 2. A. Proposed mechanism of action of Rituximab. Binding of RTX causes activation of the complement cascade (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and programmed cell death (PCD). Hypothesized mechanisms of resistance (MORs) include low CD20 expression, high serum CD20 levels, aberrant CD20 signalling, and FcγR polymorphisms. (Source: Oflazoglu *et al*. 2010). **B.** Clearance of therapeutic IgGs.

A.

B.
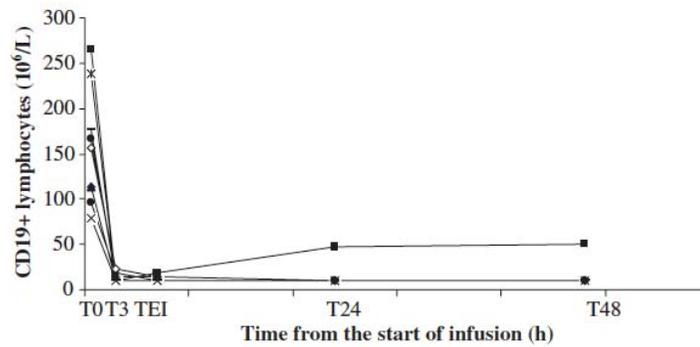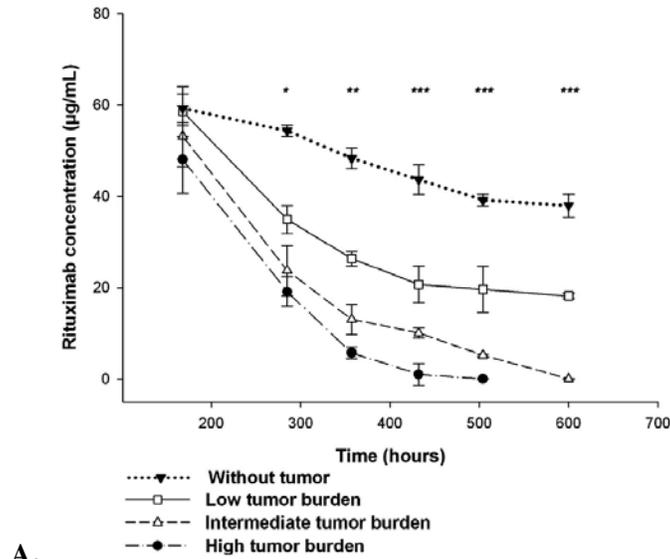
Figure 3. **A.** Results from a mouse PK/PD study to determine the effect of tumor burden on the PK/PD of RTX. The concentration of RTX in the serum is inversely proportional to the amount of tumor burden. (Source: Dayde *et al*. 2009) **B.** Change in B-cell profile over time in patients receiving RTX treatment for NHL over the course of RTX infusion. T0 = start of infusion, T3=3 hours into infusion, TEI = end of infusion, T24/48= 24/48 hours after start of infusion. Curves represent 10 individual patients. (Source: Blasco *et al*. 2008).
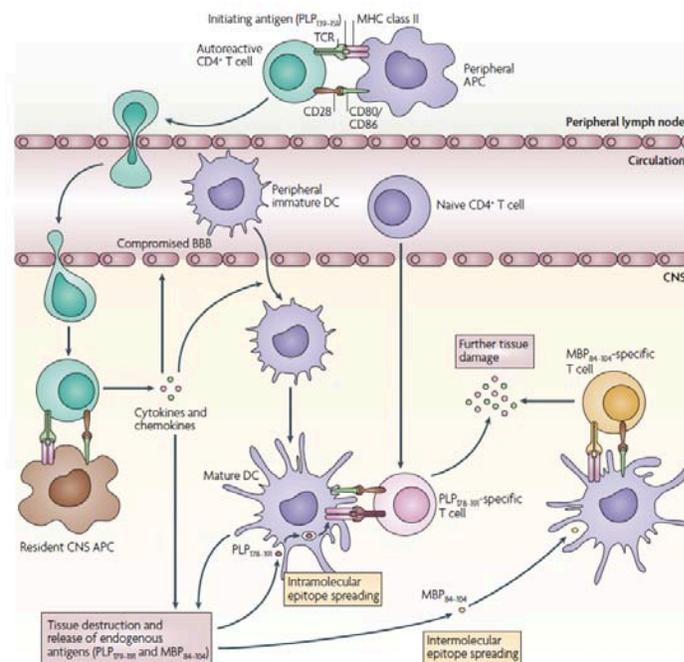
Figure 4. Disease model for Multiple Sclerosis (Miller *et al*. 2007) and proposed evidence supporting the novel role of B-cells in MS (Hartung *et al*. 2010). The current disease model for the pathogenesis of MS is shown above. T cells are activated in draining lymph nodes, enter circulation, and extravasate into the CNS. Once in the CNS, these auto-reactive T cells initiate myelin destruction and recruit more immune cells to the CNS, leading to a weakened blood-brain barrier (BBB) and a strong immune response. This primary episode leads to expansion of epitopes recognized by T cells. It is believed that B-cells produce auto-antibodies against CNS components, can form germinal centers in the intrathecal space, and help mediate myelin destruction through the production of auto-antibodies. The primary evidence for the pathogenic role of B-cells in disease is the successful treatment of MS with B-cell depleting agents such as Rituximab.
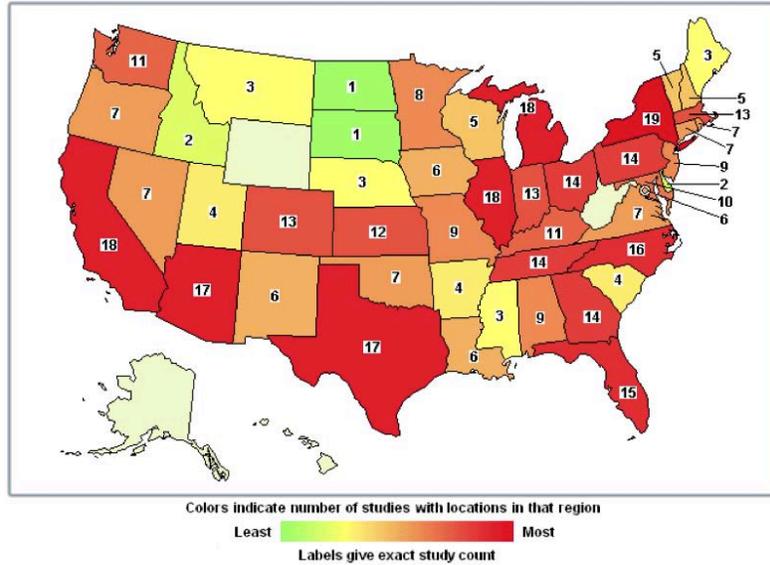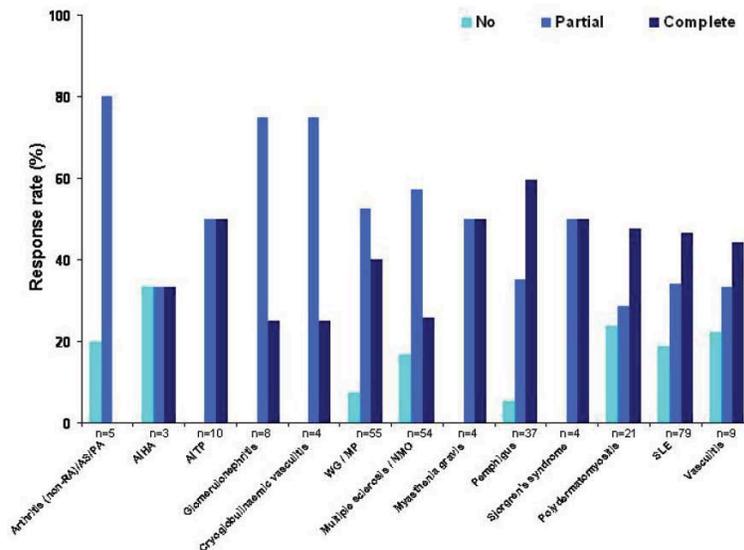
Figure 5. 80 total study sites listed for antibody therapy of MS in the United States (37 total studies). Of these, three involve OCR. Distribution of total study sites is given as a color map with a key below the map and the number of study sites listed in each state. (Source: www.clinicaltrials.gov).

Figure 6. Distribution of global response rates (full, partial, none) in patients with various autoimmune diseases that received RTX treatment. AIHA, autoimmune haemolytic anaemia; AITP, autoimmune thrombocytopenia; AS, ankylosing spondylitis; MP, microscopic polyangiitis; NMO, neuromyelitis optica; PA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; WG, ANCA associated granulomatous vasculitis. (Source: Tony *et al.* 2011)

13

MIT OpenCourseWare
http://ocw.mit.edu

20.201 Mechanisms of Drug Actions
Fall 2013

For information about citing these materials or our Terms of Use, visit: http://ocw.mit.edu/terms.