



# Use of rituximab in immunological disorders

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## Abstract

Over last few decades multiple avenues in immunology research has been opened. Recent studies have highlighted role of B cells in pathogenesis of many immunological disorders. B cells or B lymphocytes are a type of lymphocyte in the humoral immunity of the adaptive immune system that makes antibodies against invading pathogens such as viruses. Rituximab, an antibody against the B cell-expressed CD20 antigen, was the first monoclonal employed for the treatment of a glomerular disease and some other immune mediated diseases. Its uses in different immunological disorders including focal segmental glomerulosclerosis (FSGS), membranous nephritis, lupus nephritis, cryoglobulinemias, thrombotic thrombocytopenic purpura, anti-neutrophilic cytoplasmic antibody associated vasculitis, C1q nephropathy, antibody mediated renal transplant rejections, recurrent glomerular diseases in renal allograft, rheumatoid arthritis and other autoimmune neurological and muscular disorders are reviewed here in this article. Multiple searches made on related subject and articles discussing the use of rituximab in any of these diseases were reviewed for the preparation of current review. Dosage, mode of action and adverse effects of drug also been highlighted briefly.

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## Introduction

The field of immunology has progressed very fast during last few decades. Recent studies have highlighted role of B cells in pathogenesis of many immunological disorders. B cells or B lymphocytes are a type of lymphocyte in the humoral immunity of the adaptive immune system that makes antibodies against invading pathogens such as viruses. They form memory cells that remember the same pathogen for faster antibody production in future infections. B cells express B cell receptors (BCRs) on their membrane, which allow B cell to bind with a specific antigen against which antibody response is initiated. B cells divide and proliferate in response and some of these become plasma cells.

## Materials and Methods

In this review article first we searched several keywords including rituximab, use of rituximab in glomerular disorders, use of rituximab in other autoimmune disorders, CD20 antigen, role of B cells, antibody mediated rejection, recurrent glomerular diseases in renal allograft. The keywords were searched in scientific databases of PubMed/Medline, Scopus, EMBASE, EBSCO, directory of open access journals (DOAJ) and Google Scholar. We reviewed the results of the relevant papers. For this review paper, we

## Key Point

Rituximab, is an antibody against the B cell-expressed CD20 antigen, (a monoclonal antibody), has been used for the treatment of a glomerular disease and some other immune mediated diseases. Its uses in different immunological disorders glomerular and other, the promises and outcome are reviewed here in this article.

used keywords of rituximab, B cells, CD20 antigen, glomerular disorders, autoimmune neurological disorders and autoimmune muscular disorders.

## Biological actions of rituximab

Rituximab, a chimeric antibody against the B cell-expressed CD20 antigen, was the first monoclonal employed for the treatment of a glomerular disease and some other immune mediated diseases (1). Its uses in different immunological disorders glomerular and other are reviewed here in this article.

## Glomerular disorders

Till the end of millennium, the treatment of glomerular diseases has been mainly based on specific immunosuppressive agents, which were frequently associated with considerable side effects. More recently, the development of monoclonal antibodies, offered the opportunity for more selective,

treatments with lesser side effects.

### Membranous nephropathy

Membranous nephropathy is reported as the leading cause of nephrotic syndrome in adults. If untreated, about one third of affected patients reach end-stage renal disease (ESRD) in over 5-10 years after diagnosis (2).

The role of B cells in membranous nephropathy pathogenesis through autoantibody production and antigen presentation has been worked upon and it was hypothesized that rituximab may represent an ideal treatment to selectively treat the disease. Consistent with this hypothesis, in initial small size studies rituximab-induced B-cell depletion was associated with decline in urinary protein excretion and regression of immunopathologic changes of active glomerular disease (3). Rituximab has been reported to be effective when treatment with other immunosuppressants has been failed. Ruggenti et al, reported the outcomes of 100 patients with membranous nephropathy and nephrotic syndrome treated with rituximab with complete remission in 27 and partial remission in 38% patients, they have given 1-4 doses of 375 mg/m<sup>2</sup> in these patients (4).

A recent review reported that rituximab treatment was found to achieve disease remission and to stabilize or even improve renal function in membranous nephropathy patients who were at high risk of poor outcome because of persistent nephrotic syndrome. And this review recommends rituximab as better option to replace more toxic regimens as first line treatment of membranous nephropathy, at least for those patients with nephrotic syndrome unresponsive to conservative therapy (5).

### Focal segmental glomerulosclerosis

Etiology of focal segmental glomerulosclerosis (FSGS) remains unclear with emphasis on circulating factors playing role in pathogenesis, is a major cause of steroid resistant nephrotic syndrome and standard therapies not yet established. Post-transplant recurrence rate of FSGS has been reported between 15%-50% (6).

A multi-center trial evaluated the effects of rituximab therapy in 10 children and 20 adults with minimal change disease or FSGS who had shown disease recurrence after immunosuppression withdrawal, at least two recurrences over the previous year and were in steroid-induced remission for at least one month. It was observed that at one year after rituximab infusion, all patients were in remission, 18 were treatment-free and 15 never relapsed. When compared with the year before rituximab treatment, the per-patient median number of relapses decreased from 2.5 to 0.5 ( $P < 0.001$ ) during the one year of follow-up (7).

Recurrent FSGS after renal transplantation has been reported to be successfully treated with plasmapheresis and rituximab or even in plasma exchange dependent recurrent FSGS has shown good results with rituximab (6,8).

### Anti-neutrophilic cytoplasmic antibody associated vasculitis

Different small vessel vasculitis are driven by B cells and

endothelial cells activation. B lymphocyte stimulator (BlyS) released by anti-neutrophilic cytoplasmic antibody has been reported in vitro study in past (9).

Few uncontrolled studies between 2005 and 2009 has been published suggesting role of rituximab in refractory ANCA-associated vasculitides therapy (10-13).

Later two prospective trials RITUXAS and RAVE published in 2010 confirmed the role of rituximab, where it was used as induction therapy and compared with intravenous or oral cyclophosphamide, and found equally effective (14,15).

But as patients with refractory response to cyclophosphamide were excluded from these studies thus use of rituximab in these patients cannot be commented in these studies. Similarly, long term data on fertility related side effects and maintenance therapy protocols also not available while looking at these studies (14,15).

### Cryoglobulin-mediated glomerular diseases

Mixed cryoglobulins (MCs) are proteins that precipitate from cooled serum, and are said to be composed of a polyclonal immunoglobulin G (IgG) bound to another immunoglobulin that acts as an anti-IgG rheumatoid factor (RF). In type II mixed cryoglobulinemia, its monoclonal antiglobulin component, while in type III it is polyclonal. The majority of mixed cryoglobulins are found in patients with connective tissue diseases, infectious, hepatobiliary diseases, lymphoproliferative disorders, or immunologically mediated glomerular diseases (secondary mixed cryoglobulins). The etiology is not clear for about one-third of all mixed cryoglobulins, and this type of cryoglobulinemia is called "essential" (16).

Rituximab has been reported to reduce levels of antibodies which drive cryoglobulin formation (17). In a prospective trial combination of peg-interferon  $\alpha$ / ribavirin with rituximab found more effective than peg-interferon  $\alpha$ / ribavirin alone in hepatitis C associated cryoglobulin vasculitis (18). Other case reports and retrospective multi-center studies also demonstrate improvement in renal function and controlled proteinuria with use of rituximab in cryoglobulin mediated vasculitis whether associated with hepatitis C or not (19).

### Lupus nephritis

Renal involvement in systemic lupus erythematosus (SLE) is a severe disease manifestation in which thoughtful consideration of therapeutic strategies are required, especially in non-responders or in patients who frequently relapse after conventional treatment.

The standard treatment for active proliferative lupus nephritis (classes III and IV) includes corticosteroids and cyclophosphamide. This regimen has been shown to be more efficient than steroid alone (20), and the prognosis of lupus nephritis has greatly improved in the last decades. Nevertheless, the occurrences of resistant or relapsing lupus nephritis, as well as the high frequency of deleterious effects of cyclophosphamide and steroids, make the use of alternative treatments necessary. Since B cells are a

key component of dysregulated autoimmune response, it supports rationale for use of rituximab in lupus nephritis patients.

Rituximab has been used as off-label treatment for lupus nephritis during the last 10-15 years, and to date many reports on the clinical effects, including the randomized controlled LUNAR study population, have been published. Despite promising results from observational studies, with complete or partial renal response after 6-12 months in 67%-77% of patients, the LUNAR trial failed to achieve the primary endpoint and rituximab is not yet accepted as standard treatment for lupus nephritis. In these studies rituximab has mainly been used as induction therapy in combination with standard of care but the most advantageous treatment protocol is yet to be resolute. From observational studies, rituximab has been shown to be efficient in both proliferative and membranous lupus nephritis, and review of histopathology have verified improvement in renal activity (21).

### Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is rare disorder, reported incidence of disease is six cases per million per year in the United Kingdom. It is an important diagnosis to make because if left untreated mortality is as high as 90% (22). Congenital thrombotic thrombocytopenic purpura is due to an inherited deficiency of ADAMTS13, but acquired thrombotic thrombocytopenic purpura is because of the reduction of ADAMTS13 by auto-antibodies directed against ADAMTS13.

Considering auto-antibodies to ADAMTS13 as causative phenomenon immunosuppression regimens are designed to treat this disorder. A study done by Froissart et al reported shorter time of durable remission and early recovery of ADAMTS13 activity with use of rituximab in cases of thrombotic thrombocytopenic purpura (23).

### C1q glomerulopathy

C1q nephropathy was described by Jennette and Hipp in 1985, defined by noticeable C1q in glomerular immune deposits in patients with no serological evidence of SLE. It often manifests as steroid-resistant asymptomatic proteinuria or nephrotic syndrome (24). C1q glomerulopathy is a poorly understood and controversial entity with distinctive immunopathologic features. Its clinicopathologic spectrum initially defined in large series reported by Markowitz et al. C1q nephropathy is also associated with B and T cells rich tubule-interstitial infiltrates (25). A case report published by Sinha et al (26) expressed beneficial use of rituximab in resolution of C1q nephropathy larger trials to confirm this observation are still awaited.

### Kidney transplantation; antibody mediated rejection

Antibody-mediated rejection is the B-cell-mediated production of immunoglobulin G antibody against the transplanted organ. The currently available therapies for antibody-mediated rejection have had marginal accomplishment, and continual manifestations of rejection can

result in an increased risk of graft vasculopathy and perhaps graft failure at early stage requiring repeat transplantation. Rituximab, a monoclonal antibody directed against the CD20 receptor of B-lymphocytes, can be used in solid organ transplant patients for the management of antibody-mediated rejection (27).

A French group has reported similar results in terms of graft survival in two groups of patients given high dose and low dose of rituximab in antibody mediated rejection patients (28). This group used rituximab in combination with traditional anti-rejection modalities.

Recent recommendation for rituximab therapy in antibody mediated rejection is early initiation of therapy. A higher grade of tubulitis and inflammation in antibody mediated rejection are reported as negative predictors for responsiveness to rituximab therapy (29).

### Recurrent glomerular disease after renal transplant

The graft survival in children with FSGS is lower than adults with same disorder (30), and within pediatric population is lower in children with FSGS than in those with other renal diseases (31). The renal prognosis is strongly influenced by recurrence because the relative risk of graft failure is 2.25 times more in patients with recurrent FSGS as compared with patients without recurrence (32).

The management of transplant recipients with recurrent FSGS and nephrotic syndrome is difficult, controversial, and none of the multiple approaches currently available has been shown to provide sustained benefit. The most commonly used therapeutic approach is the use of plasma exchange (33). A review of the literature reported that 70% of children and 63% of adults with recurrent FSGS who received plasma exchange revealed complete or partial remission of proteinuria (34). A protective role of prophylactic plasma exchange before transplantation has also been reported. Several single-case reports pointed out the benefit of rituximab when given alone or in combination with plasma exchange (6,35), but failures were also reported (36). Currently, plasma exchange combined with high-dose calcineurin inhibitors along with rituximab or without this agent, seems to be the most promising approach, but further controlled trials are needed to define the most favorable therapeutic regimens to control recurrence of FSGS (37).

Rituximab has shown very promising effects in patients with idiopathic membranous nephropathy in native kidneys (38) and has also been reported successful in anecdotal cases of post-transplant IMN recurrence (39). In a recent study, eight patients with recurrent idiopathic membranous nephropathy and a mean proteinuria of 4.5 g/d were given two separate doses of one Gm at 2 weeks apart. Twelve months later, 35% of patients had a complete remission and another 40% shown a partial remission. After 2 years, one patient had relapsed (40).

Dense deposit disease has a very high risk of recurrence (approaching 100%). The successful treatment of an established recurrence of dense deposit disease is complex, so preventive management based on precise assessment

of the underlying mechanism accountable for the membranoproliferative glomerulonephritis is of value. Patients with complement dysregulation (e.g., factor H deficiency) should receive fresh frozen plasma before and after grafting, plasma exchange (with fresh frozen plasma replacement) and/or rituximab might also be useful in patients with a neutralizing autoantibody to factor H (41).

### Rheumatoid arthritis

Rheumatoid arthritis is a chronic systemic autoimmune disease characterized by inflammation of joints. The disease has been a significant cause of disability in affected person. Over the last 3 decades after the introduction of methotrexate in the 1980s, there have been remarkable improvements in patient outcomes (42). The advanced therapies targeting tumor necrosis factor (TNF) and interleukin-1 has resulted in further improvement in outcomes. Further progress in therapy targeting towards B-cell depletion is an effective measure. The titers of rheumatoid factor were shown to decrease two-to-threefold after treatment with rituximab in some of published studies (43,44).

### Autoimmune neurological disorders

During the past three decades, investigations into neuroimmunological diseases of the central nervous system (CNS)—and to a lesser degree the peripheral nervous system—have centered primarily on the roles of activated, cytotoxic and immune-regulatory T cells rather than B cells. B cells have been reported to play a fundamental role in the pathogenesis of various autoimmune neurological disorders, not only as precursors of antibody-producing cells, but also as vital regulators of the T-cell activation process through their participation in antigen presentation, production of cytokines, and formation of ectopic germinal centers in the intermeningeal spaces (45).

Over the past few years, however, convincing data on the roles of B cells as sensors, coordinators and regulators of the immune response (46) have supported the view that B cells and autoantibodies are essential for activating T cells and/or mediating tissue injury in a number of disorders of the CNS and peripheral nervous system.

In the context of autoimmune neurological disorders, B cells have customarily been associated with the making of autoantibodies from plasma cells, the end products of B-cell differentiation (47).

In most autoimmune neurological disorders, however, the autoantibodies are aimed against cytosolic antigens and might not be straightforwardly involved in tissue injury. In such cases, B cells may still participate in the autoimmune process through antibody-independent mechanisms that include antigen presentation, costimulation, cytokine production, and coordination of T-cell functions (48,49). Activated B cells are also as efficient as T cells at producing cytokines—most notably interleukins (IL-1, 4, 6, 10, 12, 23 and 16), TNF and the chemokines macrophage inflammatory protein 1 $\alpha$  (MIP1 $\alpha$ ) and MIP1 $\beta$  (50,51).

Specific markers, such as CD20, CD27, BAFF-R (B-cell-activating factor receptor), CD38 and CD138, identify the

transitional phases of B cells from stem cells to plasma cells (45).

### Multiple sclerosis

In multiple sclerosis, B cells and antibodies are involved to varying degrees at different stages of the disease. Interactions between the homeostatic chemokines (CXC), chemokine ligand (CXCL) 13, CXCL10 and CXCL12 secreted from the endothelial cell wall and their respective receptors on B cells (52) are fundamental for B-cell homeostasis within the lymphoid follicles and in the brain. These molecules found up-regulated in the brains of patients with MS, allowing the enrollment and transmigration of antibody-producing B cells into the brain (53).

In secondary progressive multiple sclerosis, activated B cells form germinal centers in the lymphoid tissues and in the intermeningeal spaces, where they undergo the same stages of differentiation as in the periphery (54).

B cells generate inflammatory mediators that can stimulate plasma cells for in situ creation of immunoglobulins. The production of intrathecal immunoglobulins (which stay throughout life as oligoclonal bands) in all forms of multiple sclerosis indicates a central role for activated B cells and plasma cells in this disease.

In patients with multiple sclerosis, 24 weeks of treatment with rituximab was shown to deplete B cells from the cerebrospinal fluid (CSF) and suppression of further B-cell activation, but it did not affect the intrathecal synthesis of oligoclonal IgG bands originated from long-lived plasma cells (55).

A multicenter clinical trial of 104 patients with relapsing-remitting multiple sclerosis, a 58% relative reduction in the proportion of patients who experienced a relapse was noted after 24 weeks of therapy. And remarkable reduction in the mean number of gadolinium-enhancing MRI lesions (56).

In an open-label trial of 26 patients who were treated with two courses of rituximab given at 6 months interval and followed for up to 72 weeks after initialization of treatment, reductions in relapses of clinical symptoms and lesions on MRI were noted, suggesting long-lasting benefit (57).

### Myasthenia gravis

Myasthenia gravis is a prototypic B-cell-mediated autoimmune disease caused by antibodies against the muscle acetylcholine receptors. Evidence from around 20 case reports suggests that rituximab is useful in most patients, but a controlled study has not yet been done (58-61).

### Neuromyelitis optica

Neuromyelitis optica (NMO) is an inflammatory CNS disorder that affects the optic nerves and the spinal cord. It typically presents with myelitis and optic neuritis, and is characterized by varying degrees of sensory motor disturbances, bladder-bowel dysfunction and visual loss. In NMO, autoantibodies, collectively termed NMO-Ig, bind to cerebral microvessels (62). In an open-label study, six out of eight patients with NMO became relapse-free after

one year of rituximab therapy, with a drop in relapse rate from 26 to zero attacks per year (63).

### Paraneoplastic neurological disorders

Patients with paraneoplastic neurological disorders have circulating antibodies against a diversity of antigens that are expressed in brain and in cancer cells, both. There is evidence that B cells, plasma cells and cytotoxic T cells cross the blood-brain barrier, and antibodies are synthesized intrathecally. Rituximab, along with IVIG or adrenocorticotrophic hormone (ACTH), improved the ataxia severity scores, ameliorated myoclonus and the rate of clinical relapse declined in 81% of 16 children with opsoclonus-myoclonus syndrome and the numbers of clonally expanded B cells found reduced in the CSF (64).

### Chronic autoimmune neuropathies

The chronic autoimmune neuropathies include a spectrum of largely demyelinating neuropathies, the most common are chronic inflammatory demyelinating neuropathy (CIDP), multifocal motor neuropathy (MMN) and IgM anti-myelin-associated glycoprotein (IgM-MAG) neuropathies. B cells in the pathogenesis in these conditions are evident by the deposition of immunoglobulins and complement on the patients' nerves, and the complement-fixing antibodies against MAG and gangliosides (65). In an open series of 21 patients with positive IgM antibodies to gangliosides, rituximab improved symptoms in 61% of the patients, as reported after 6 months therapy, and the benefits were maintained for at least up to 2 years (66).

### Inflammatory myopathies

There are three main subsets of inflammatory myopathies; polymyositis, dermatomyositis and inclusion body myositis. In all these forms of the disease, B cells and plasma cells are present in the muscle tissues, and in dermatomyositis immunoglobulins are deposited on endomysial capillaries (51). In 10 patients with polymyositis or dermatomyositis who had responded poorly to current therapies, rituximab shown an increased or normalized muscle strength in 80% of cases. Serum levels of creatine kinase and the required prednisone dose were reduced at the same time (67).

### Mechanism of action

Rituximab depletes B cells through three mechanisms, antibody-dependent cellular cytotoxicity, where antibody-coated cells bind to the Fc receptors of macrophages or natural killer cells; activating the membrane attack complex on B cells (complement-dependent cytotoxicity); and inducing apoptosis by changing the lipid rich environment on the CD20<sup>+</sup> B-cell membrane (45).

### Dosage

Rituximab can be administered intravenously at a dose of 375 mg/m<sup>2</sup>, given every week for 4 occasions, or two doses of 1 g infusions, given at fortnightly intervals (Total 2 g). The average half-life of the drug after completion of an infusion is 21 days. The infusions can be repeated after 6-12

months.

### Adverse effects

The main adverse effect has been infusion reactions which most commonly occur during the first infusion. Patients may experience nausea, itchiness, rash, hot flushes, and both hyper or hypo in blood pressure can occur. It is very unusual for patients to stop the infusion due to these problems and these symptoms become much less severe following the first infusion of rituximab. There is an interesting finding that in the longer term there does not appear to be a great increase in infections or other major side-effects (68).

Rarely reported adverse effect is progressive multifocal leukoencephalopathy (PML), which can damage the brain and spinal cord. Fatal liver failure, respiratory failure and heart failure also been reported in very rare instances (69).

### Author's contribution

RN is the single author of the paper.

### Conflicts of interest

The author declared no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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