Rituximab in immunologic glomerular diseases

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Keywords: rituximab, glomerular diseases, transplant, rejection

Experimental data suggest that the B-cell antigen CD20 may play a significant role in the pathogenesis of many diseases including glomerular diseases. These and other findings underpin the central concept of B-cell-depleting therapies that target CD20 antigen as treatments for lupus nephritis, idiopathic membranous nephropathy, focal segmental glomerulosclerosis, cryoglobulinemic glomerulonephritis, antibody mediated renal allograft rejection and recurrent glomerulonephritis in renal allograft. Use of rituximab as a B-cell depleting therapy has been associated with clinical improvement and has emerged as a possible adjunct or alternative treatment option in this field of nephrology.

Introduction

Substantial progress in the field of clinical immunology has been achieved with the use of genetic and immunologic tools. Given the role of B cells in the pathogenesis of many immunological processes, attention has been focused on the development of monoclonal antibodies (mAbs) that target these cells. Central to the concept of B-cell targeted therapy in these diseases is the evidence that B-cell clones and their autoantibody products are engaged in immunological cascades that do not require T-cell auto-reactivity. It is plausible that the interruption of such cycles would restore immune tolerance and might allow sustained benefit. Recently, there has been tremendous interest specifically in B-cell depletion therapy in auto-immune diseases. Such therapy has been associated with clinical improvement in many conditions associated with autoantibody production such as rheumatoid arthritis, systemic lupus erythematosus (SLE), idiopathic thrombocytopenia, anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) and kidney diseases such as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), idiopathic membranous nephropathy (MN), cryoglobulinemic glomerulonephritis, antibody mediated renal allograft rejection and recurrent glomerular diseases in renal allograft.1-10

Rituximab, originally developed by IDEC Pharmaceuticals, is currently co-marketed by Biogen Idec and Genentech in the US, by Roche in Canada and the European Union, and by Chugai Pharmaceutical and Zenyaku Kogyo in Japan. Rituximab, sold under the trade names Rituxan® and MabThera®, is a chimeric mAb. Structurally, the binding regions from the original murine monoclonal antibody (mAb) basically retain the murine CD20-binding Fab regions, but uses a human IgG1 heavy chain and kappa light chains, are fused to human IgG1 heavy chain and human kappa light-chain constant regions. Thus, rituximab retains the murine CD20-binding Fab regions, but uses a human Fc portion. The structure allows rituximab to be less immunogenic, i.e., it induces less human anti-mouse antibody response in patients than the murine version. The Fc portion contains the effector aspects of the molecule, e.g., complement activation and attraction of cytotoxic cells.

Evidence for multiple mechanisms of rituximab action has been reported. The events that lead to cell killing following antibody binding to CD20 are multifactorial. These events influence both the cytotoxicity of rituximab and development of resistance against rituximab.11 CD20 also acts as a calcium channel,12 either directly or by activating calcium channel, and is associated with a number of protein kinases, including lyn, fyn, lck and p75/85 kinases.13 CD20 engagement leads to activation of phospholipase Cγ via src-family kinases and other downstream events, including MAP kinase activation, viz., JNK, ERK and p38MAPK.14
Rituximab mode of action: apoptosis and ADCC. Rituximab mediated apoptosis is thought to be a consequence of caspase-3 activation. Complement activation by the Fc portion of the antibody leading to cell lysis is another mode of action of rituximab. Rituximab also induces ADCC mediated by a variety of effector cells (natural killer cells, granulocytes and macrophages). ADCC in the presence of rituximab represent killing of B cells by effector cells that are activated by binding to the Fc portion of the chimeric anti-CD20 molecule.

Steroid-Resistant and Steroid-Dependent Nephrotic Syndromes

Steroid resistance and steroid dependence constitute a major problem in the treatment of minimal-change disease (MCD) and FSGS. MCD has been postulated to result from a circulating T-cell factor that causes podocyte cytoskeleton disorganization. Recently, persistent CD80 expression in podocytes, induced by Toll-like receptors, has been suggested to be a causative factor.\textsuperscript{19} In addition to T cells, B cells also may play an important role in the pathogenesis of idiopathic nephrotic syndrome. Altered expression of B lymphocyte surface immunoglobulins in minimal change nephrotic syndrome and focal glomerulosclerosis have been reported.\textsuperscript{20} Case series have suggested that rituximab may maintain disease remission in steroid-resistant and steroid-dependent nephrotic syndrome patients. In a multicenter study of 22 cases of severe steroid- or cyclosporine-dependent nephrotic syndrome (16 MCD, others FSGS), treatment with rituximab resulted in the withdrawal of immunosuppressive therapies in 85% of the patients without relapse of proteinuria or increasing other immunosuppression therapies.\textsuperscript{21} Others have reported that a single dose of rituximab may be effective for refractory steroid-dependent nephrotic syndrome in reducing frequency of relapses and increasing the steroid-free period; however, the effects were transient in most of the patients.\textsuperscript{22} While rituximab was safe and effective in inducing and maintaining remission in a significant proportion of adult\textsuperscript{23} and children\textsuperscript{24} with steroid-dependent nephrotic syndrome, a second treatment was necessary in most children to maintain long-term (up to 18 mo) B-cell depletion. A small number suffered from reversible cytokine shock. Recently, a randomized controlled trial reported that a strategy based on rituximab and lower doses of prednisone and calcineurin inhibitors was noninferior to standard doses of these agents in maintaining 3-mo proteinuria as low as baseline or up to 1 g/d greater in children with steroid- and calcineurin-dependent nephrotic syndrome (MCD 19, FSGS 17, other 18).\textsuperscript{25} In children with difficult-to-treat steroid-dependent nephrotic syndrome who had previously received levamisole, cyclophosphamide or mycophenolate mofetil, and then were treated with either rituximab or tacrolimus and followed for 12 mo, treatment with 2–3 doses of rituximab was as effective as 12 mo of therapy with tacrolimus in reducing relapsed rates and steroid use.\textsuperscript{26} FSGS, which may require repeated courses of steroid therapy or additional long-term immunosuppression, represents another difficult therapeutic challenge. Only 50% of steroid resistant FSGS patients achieve long-term remission even with intensive immunosuppression and plasma exchange (PEX).\textsuperscript{27–29} A number of case reports and observational studies point to the beneficial effects of rituximab as a rescue therapy in children with steroid/
cyclosporine dependent or steroid resistant FSGS. In renal transplant patients who are at high risk for recurrent FSGS, treatment with rituximab was able to prevent disruption of the actin cytoskeleton and podocyte apoptosis induced by patient sera, suggesting that modulation of sphingolipid-related proteins (independent of B-cell mechanism) plays a role in FSGS.15 Pediatric patients with primary FSGS seem to have positive responses to treatment with rituximab in achieving complete or partial remission of nephrotic remission.30-34 On the contrary, Spanish Group for the Study of Glomerular Diseases (GLOSEN) reported that rituximab was successful in improving renal function and achieving a sustained reduction in proteinuria in two of eight adult patients with FSGS.35 No differences were observed in CD20+ B lymphocyte count among the responder and non-responders. It is therefore plausible that rituximab may induce anti-proteinuric effect through mechanisms independent of B-cell depletion.

Idiopathic Membranous Nephropathy

Idiopathic membranous nephropathy (MN) is an immune-mediated disease that results from the deposition of IgG and complement components on the sub-epithelial layer of the glomerular basement membrane. The discovery that M-type phospholipase A2 (PLA2) receptor is a target antigen in idiopathic MN has provided therapeutic opportunities for the use of rituximab.36 Treatment of MN with rituximab has been associated with a fall in PLA2-receptor antibody levels followed by decreases in proteinuria, whereas an increase in PLA2-receptor antibody levels was associated with an increase in proteinuria.37,38 In a systematic review of 21 case reports or case series without controls where 50 of 85 published cases were from one center where rituximab was used as primary immunosuppression for idiopathic MN, the use of rituximab was associated with a 15–20% rate of complete remission and a 35–40% rate of partial remission with minimal adverse events.3 Rituximab-induced remission has been demonstrated to be associated with restoration of sodium homeostasis and kidney hemodynamics, and regression of the glomerular changes underlying proteinuria.39 Rituximab appears to promote sustained disease remission in patients otherwise predicted to progress to end stage renal disease.40,41 Rituximab can also be an effective tool to overcome dependence on calcineurin inhibitors in idiopathic MN patients with long-term calcineurin inhibitor dependence.42 Use of rituximab must be carefully considered because spontaneous remission is common among patients with nephrotic syndrome from idiopathic MN and carries a favorable long-term outcome with a low incidence of relapse.43

Lupus Nephritis

The rationale to target B cells in lupus lies in its production of antibodies targeting self-antigens to form immune complexes that deposit to tissues and activate the inflammatory process. Rituximab has been used in SLE, both with or without renal involvement. In moderate-to-severely active SLE without renal involvement, the effect of rituximab was not different than placebo in achieving and maintaining the primary endpoints of a major clinical response, a partial clinical response, or no clinical response at week 52 assessed using the British Isles Lupus Assessment (BILAG) index organ system scores.44 This randomized, double-blind, placebo-controlled, multicenter North American study (Exploratory Phase II/III SLE Evaluation of Rituximab-EXPLORER trial) demonstrated that African-Americans and Hispanics achieved a significantly higher major clinical responses compared with other groups, and that rituximab effected a sustained depletion of CD20-positive peripheral B lymphocytes and anti-double-stranded DNA (ds DNA) and improvement in complement factor levels throughout the study period. Others have reported a decrease in CD21, CD40 and BR3 on the residual B cells, percentage of CD69+ CD4+ T cells and serum tumor necrosis factor levels and a shift in the Th1/Th2 balance of CD4+ T cells gradually toward a Th1 type with rituximab therapy.45

Data on the effectiveness of rituximab for remission induction in lupus nephritis (LN) is scarce. Complete remission was successfully induced with rituximab alone in several small studies with favorable response at 24 mo.6,47 In another series of patients with class III/IV/V LN who received rituximab induction therapy and mycophenolate mofetil (MMF) maintenance therapy, complete or partial remission (78%) with a sustained response (67%) was achieved at one year; a decrease in proteinuria and reduction in maintenance dose of steroids and an increase in serum albumin were also observed.48 Rituximab monotherapy appeared to be effective as induction therapy in LN and had similar effects on clinical, laboratory and renal histological parameters and duration of B-cell depletion at 48 weeks in combination therapy with cyclophosphamide.49 A recently published exploratory analysis, which was performed to determine the frequencies of disease flares of varying intensity in patients who achieved low disease activity (BILAG C or better in all organs) at some point during the above-mentioned EXPLORER study and to evaluate the incidence of prednisone rescue when flares occurred, failed to show significant additional effects of rituximab compared with standard induction treatment with azathioprine/MMF and steroids.50 Rituximab appears to work as a rescue therapy for some patients with relapsing or refractory LN. The combination of cyclophosphamide with rituximab has been reported to achieve clinical remission and lasting depletion of CD20+ cells and anti-ds DNA titers.31,52 The combination of rituximab and MMF also appears to be beneficial in relapsing LN with subnephrotic proteinuria.53 In an open-label, multicenter study of 15 patients with active and refractory SLE, 64% of the patients achieved complete or partial clinical response of BILAG scores.34 The clinical response was also associated with improvement in histopathologic class of nephritis with decrease in renal activity index (from 6 to 3) and reduction in the number of CD3, CD4 and CD20 cells in the renal interstitium on repeat biopsy.55 In a study of safety and efficacy of off-label use of rituximab in patients with severe, refractory systemic autoimmune diseases including SLE (54.6% of participants), complete and partial response were achieved in 51 and 26%, respectively.56 SLE was one of diseases that responded most favorably to rituximab. Rituximab in such cases must be used with other therapies,
although maintenance steroids are not necessary. However, others have cautioned that good response to rituximab as induction therapy for refractory LN has not been associated with long-term favorable results. Furthermore, patients with rapidly progressive glomerular diseases, black ethnicity or hypoalbuminemia did not respond to rituximab in these studies. The achievement of B-cell depletion 1 mo after rituximab appears to be a strong predictor of renal response. Of cautionary note is the development of serum sickness with an elevated level of human anti-chimeric antibody (HACA) following treatment with rituximab, occurring in 1–20% of patients and more common with autoimmune conditions. Other have reported that approximately a third of the patients receiving rituximab may develop HACA titers, which correlate with poor B-cell depletion and may explain the variability of responses in patients with LN.

**Anti-Neutrophilic Cytoplasmic Antibody-Associated Vasculitis**

AAVs comprise different forms of small vessel vasculitis characterized by B-cell driven autoimmune processes and endothelial cell activation. In vitro studies have demonstrated that anti-neutrophilic cytoplasmic antibodies specifically cause the release of B lymphocyte stimulator (BlyS) from activated neutrophils, which can support B-cell survival. BlyS protein regulates B-cell activation and differentiation. Uncontrolled studies had suggested for years that rituximab may be an effective remission induction therapy for refractory AAV. Two prospective randomized trials have since confirmed that rituximab is not less effective than cyclophosphamide for induction therapy for active AAV. Rituximab-based regimen was not superior to standard intravenous cyclophosphamide in the rituximab vs. cyclophosphamide in AAV (RITUXVAS) trial, nor was it inferior to daily oral cyclophosphamide for induction in the rituximab in AAV (RAVE) trial. In the RITUXVAS trial, newly diagnosed AAV with renal involvement patients were assigned via 3:1 randomization to a standard glucocorticoid regimen plus either rituximab vs. intravenous cyclophosphamide for 3 to 6 mo followed by azathioprine. Sustained remission rates of 76% and 82% (p = 0.77) at 12 mo were achieved in the rituximab vs. control group. For the primary safety endpoint, severe adverse events occurred at a similar rate; 42% in the rituximab vs. 36% in control group (p = 0.77). In the RAVE trial, rituximab was compared with standard cytotoxic therapy with oral cyclophosphamide for the induction of complete remission by 6 mo in patients with severe AAV. Complete remission was achieved in 63% in the rituximab group vs. 53% in the control group, a result that met the criterion for non-inferiority (p < 0.001). Remission was achieved with similar frequency in patients with newly diagnosed disease (rituximab 60% and control 65%) and in relapsing disease (rituximab 67%). Rituximab was equally effective as cyclophosphamide in the treatment of patients with major renal disease or alveolar hemorrhage, and there was no consistent pattern to organ-system involvement in those who failed to achieve remission. One-year mortality was high in elderly patients with advanced renal failure in the RITUXVAS trial and a third of patients did not achieve remission. The adverse events were similar in both studies; however, the potential for rituximab as a standard of care may have to be tempered until long-term adverse effects relating to fertility and malignant conditions are clarified. Rituximab has been successfully used as maintenance therapy in AAV in a small series of patients, but the RITUXVAS and RAVE trials did not assess this issue. Response to rituximab may also be affected by the disease modifying effect of long-term low-dose steroids. Of concern is that the most severe adverse events and deaths occurred in the first 12 weeks after the onset of treatment in the RITUXVAS trial. The investigators have suggested that strategies to reduce the early high dose of steroids may improve the safety of vasculitis treatment. There was also a nonsignificant yet higher rate of malignant conditions that may or may not be attributable to rituximab because malignant conditions are frequently associated with vasculitis at the time of diagnosis, most patients have been exposed to multiple drugs known to be associated with an increased risk of cancer, and rates of cancer occurrence is similar to that observed with other treatments for AAV. It is not known whether patients who are refractory to cyclophosphamide would benefit from rituximab as these patients were excluded from study. However, previous response to cyclophosphamide did not preclude response to rituximab. Recent retrospective data suggest that in patients with refractory granulomatous AAV, granulomatous manifestations such as orbital granuloma and pachymeningitis may be responsible for failure of response/progress.

Rituximab appears to have fewer fertility-related adverse events, but long-term data are not available. Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal AAV has been reported; however, its necessity except in life threatening AAV has been questioned. An unresolved issue is the need for maintenance therapy and the timing of retreatment with rituximab to prevent relapses.

**Cryoglobulin-Mediated Glomerular Diseases**

Rituximab reduces antibody levels that drive cryoglobulin formation and thereby reduces clinical symptoms of vasculitis. A review of 119 cases of cryoglobulinemic vasculitis where rituximab was applied mostly after failure of other treatments, significant reduction in levels of rheumatoid factor, cryoglobulins and IgM were reported. Complete, partial and no responses were noted in 60%, 23% and 17% respectively. The incidence of adverse effects was 19%, mostly associated with high baseline levels of cryoglobulins, dose of rituximab infusion (1 g) and complement activation. In a prospective trial, rituximab plus peg-interferonα/ribavirin was more effective than peg-interferon-α/ribavirin in hepatitis C-related mixed cryoglobulinemia. Rituximab has also reported to be efficacious in a single case report of hepatitis C-negative therapy-resistant essential mixed cryoglobulinemia with renal and cardiac failure. Retrospective data from a large multicenter cohort study also demonstrated improvement in renal function and proteinuria in mixed cryoglobulinemic patients treated with rituximab irrespective of hepatitis C virus (HCV) status. Rituximab has been effectively used in cryoglobulin-related renal dysfunction in renal transplant patients, albeit at the
expense of infectious complications due to chronic immunosuppression. Cryoglobulinemic glomerulonephritis derived from Waldenström’s macroglobulinemia was successfully treated by rituximab-CHOP (cytoxan, vincristine, adriamycin and prednisone) and tandem high-dose chemotherapy with autologous peripheral blood stem cell transplantation. Of interest, acute renal failure can also occur secondary to severe type I cryoglobulinemia following rituximab therapy for Waldenström’s macroglobulinemia and post treatment monitoring of cryoglobulin levels are prudent. Another entity that responds well to rituximab is non-cryoglobulinemic glomerulonephritis with monoclonal Ig deposits associated with membranoproliferative glomerulonephritis (MPGN) and MN. Treatment of hepatitis C-related cryoglobulinemia is associated with transiently increased expression of HCV RNA and may be followed by hepatic flare, possibly immune-mediated, which can be life threatening in cirrhotic patients. Direct and indirect roles for B cells have been suggested to explain these observations. Results from in vitro models suggest that HCV is released from B cells in the presence of rituximab and may contribute to the increased viral load observed in patients. Further elucidation of the mechanisms involved and effect on clinical outcomes need clarification.

**C1q Glomerulopathy, Nonamyloid Fibrillary and Immunotactoid Glomerulopathies**

C1q nephropathy is characterized by mesangial deposition of immunoglobulin and complement with C1q dominance or co-dominance with IgG or IgM, absence of clinical and laboratory evidence of systemic lupus erythematosus and inconsistent response to immunotherapy. C1q nephropathy is also associated with B- and T-cell-rich tubulointerstitial infiltrates. Anecdotal cases of resolution of clinical and pathologic features of C1q nephropathy has been reported after rituximab therapy, but controlled trials are not available. A single case series of 3 patients with fibrillary glomerulonephritis who were treated with rituximab for nephrotic-range proteinuria have been reported. Treatment with rituximab and standard antiproteinuric therapy with renin-angiotensin system blockade affected a decrease in proteinuria and preservation of kidney function throughout the 27-mo follow-up period.

**Thrombotic Thrombocytopenic Purpura**

Thrombotic thrombocytopenic purpura (TTP) is associated with excessive systemic platelet aggregation due to accumulation of ultralarge multimers of von Willebrand factor related to severe deficiency of the cleaving protease, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). The rationale for immunosuppressive therapy of TTP was established by observations that TTP may be caused by autoantibodies to ADAMTS13. Patients with high-titer autoantibodies to ADAMTS13 may have a higher mortality, and survivors may require prolonged PEX therapy in spite of adjunctive glucocorticoid treatment. A Phase 2 study of the safety and efficacy of rituximab given within 3 d of acute TTP admission with standard therapy (PEXs and steroids) suggests a benefit of rituximab therapy given at acute presentation even in patients presenting with the severest disease phenotype. Significant reduction in the number of inpatient days, mean number of PEX treatments until remission, and decrease in relapse rates were noted compared with historical controls who did not receive rituximab. However, the observed benefits were lower in nonwhites compared with white patients, which requires further investigation. The efficacy and safety of rituximab in 23 adults responding poorly to standard therapy (PEX plus glucocorticoids) for severe autoimmune TTP were compared with 53 historical controls by the French Thrombotic Microangiopathies reference center group in an open-label prospective study. Treatment with rituximab was associated with a shorter time to durable remission, early recovery of ADAMTS13 activity and trend toward fewer exacerbations within 1 y. Complete B-cell depletion was achieved within 4–8 d, but the onset of rituximab effect (sustained normalization of platelets) was evident only at 12 ± 6.7 d, suggesting persistent anti-ADAMTS13 antibody or that rituximab affects precursor B cells and not antibody-forming cells. The time to rituximab effect was 12 d in the above-mentioned rituximab in acute TTP study that demonstrated benefit with rituximab. Nevertheless, these observations highlight the possibility that rituximab may fail to prevent early death or deterioration in patients with severe initial presentation at diagnosis.

**Kidney Transplantation: Antibody-Mediated Rejection**

B cells play important roles in antigen presentation, T-cell activation and alloantibody production that drive transplant rejection. A variety of new treatments that include rituximab are currently being explored to deplete B-cell populations in the hopes of reducing acute rejection episodes and preserving long-term graft survival. CD20+ cells were shown to be present in large numbers in renal allograft with steroid-resistant rejection episodes. Becker et al. reported that a single dose of rituximab was successful in reversing steroid-resistant in 24 of 27 kidney transplant patients. Shortly thereafter, Genberg et al. showed that, in ABO-incompatible kidney transplants, single-dose rituximab obviated the need for splenectomy; the overall graft survival was 86.7% at 3 y (comparable to the ABO-compatible control group). In a prospective, double-blinded, multicenter randomized trial comparing rituximab (n = 68) and placebo (n = 68) in kidney transplant recipients, the authors also showed a trend toward numerically fewer rejection episodes in rituximab arm (rituximab vs. placebo: 8 vs. 12; p = 0.317). All patients also received tacrolimus, MMF and steroids. A recent study attempted to compare single-dose rituximab with daclizumab, in non-sensitized kidney transplant patients (n = 120) but the study was halted due to high acute rejection episodes in the rituximab arm (rituximab vs. daclizumab: 83% vs. 14%, p = 0.01). The current data, therefore, suggest that rituximab may be useful as an induction agent in high-risk patients who are ABO-incompatible recipients or who experience steroid-resistant rejection episodes.
Antibody-mediated rejection (AMR) is a unique and often severe form of allograft rejection. The pathophysiology of AMR suggests a prime role of antibodies, B cells and plasma cells, and other effector molecules including complement systems. The immediate loss of allograft from hyperacute AMR is rare because of advancement in anti-HLA antibody detection and ABO matching. However, new-onset AMR related to increases in donor-specific antibody (DSA) can occur within hours of transplantation resulting in rapid allograft dysfunction. The established pathological criteria for diagnosing AMR include complement fragment C4d deposition in peritubular capillaries, pathological features of inflammation and allograft dysfunction.32 Recently, Vo et al. reported their experience with 123 highly sensitized patients who received kidney transplant after desensitization.33 Twenty-two patients who developed AMR were treated with combination of steroids, intravenous immunoglobulin and rituximab. The authors reported 73% survival rate in this high risk group (6/22 patients lost their allograft due to severe AMR). Kaposztas et al. retrospectively compared PEX with rituximab (n = 26) and PEX without rituximab (n = 28) in patients with AMR. Two year graft survival was significantly better in rituximab treated group (90% vs. 60%; p = 0.05).26 Others have reported complete reversal of AMR in all patients (7/7) with single low dose of rituximab (500 mg).35

Recurrent Glomerular Diseases in Renal Allograft

Glomerular diseases are the cause of end stage renal disease (ESRD) in 30% of kidney transplant recipients. In these patients, the rate of clinical recurrence of glomerular diseases ranges between 0–100%.96-98 and recurrent glomerular diseases are considered to be the third most common cause of progressive renal allograft failure. All forms of primary glomerular diseases may recur after kidney transplantation and may negatively impact of the allograft survival. In a study that included almost 5,000 transplant recipients, the mean time to recurrence was 475, 594, 664 and 846 d for FSGS, MPGN, MGN and IgA nephropathy (IgAN), respectively.99 Steroids, PEX and various other immunosuppressive agents have been tried to halt the progression of recurrent glomerular diseases. As in the cases of native kidneys affected by glomerular diseases, rituximab, when administered with other immune modulating therapies, has also been shown to reduce proteinuria and prevent progression of recurrent GN. However, because of the lack of prospective, randomized trials in these diseases in renal allograft, recommendations come only from case reports and single center experiences. Six consecutive patients who developed recurrent glomerular diseases (FSGS 3, one of each with MPGN type I, MGN and IgAN) 3–72 mo post-transplant were treated with rituximab, pulse steroids or maximizing mycophenolate mofetil and calcineurin inhibitor therapy. After a follow-up of 9 mo, there were significant decrease in proteinuria (7.2 ± 4.4 g to 1.4 ± 1.5 g; p = 0.04) and improvement in graft function as measured by glomerular filtration rate (31.2 ± 13.1 to 42.5 ± 21.7 ml/min; p = 0.07).100

Among all glomerular diseases, FSGS has a high chance of recurrence especially when a first transplant fails due to recurrent disease; the risk of recurrence in the second transplant approaches 80–100%.101 No controlled studies have been performed yet to address the management of recurrent FSGS. Mixed reports of the efficacy of rituximab in renal transplantation patients with recurrent FSGS have been reported in reference 102–105 of the different approaches, only PEX with rituximab was associated with prolonged remission.15,105-107 In a recent study of 41 patients at high risk for recurrent FSGS, 27 of whom were treated with rituximab at time of kidney transplant, rituximab at time of kidney transplant was shown to prevent recurrent focal segmental glomerulosclerosis by modulating podocyte function in a sphingomyelin phosphodiesterase acid-like 3b-dependent manner.35 Despite the paucity of data, combination of PEX and rituximab remains an acceptable treatment in patients with post-transplantation recurrent FSGS in many instances. Successful treatment of collapsing FSGS in two children with a combination of rituximab, steroids and cyclosporine has been reported in reference 108.

The incidence of biopsy proven de novo or recurrent MGN has been reported to occur in 10–30% of patients in various series. Grant loss in those who develop recurrent or de novo GN is variable. Hariharan et al. reported a multi-center review of 4,913 patients and showed that MGN occurred in 16 cases with overall graft loss of 44% at 5 y and a kidney half-life of 1,193 d.99 Because of recent reports demonstrating beneficial effects of rituximab in idiopathic MGN in native kidneys (vide supra), similar approach has been utilized in the setting of recurrent MGN. Spranglers et al. reported their experience in four patients with recurrent MGN who received different doses of rituximab.100 After the first course of rituximab, proteinuria worsened (n = 1), stabilized (n = 1) and improved (n = 2). Subsequent courses of rituximab resulted in improvement in proteinuria in non-responders. All patients continued to have stable renal function 16 mo after the last administration of rituximab. In another report, eight patients with recurrent MGN with progressive increase in proteinuria (211 mg/day to 4,489 mg/day) were treated with rituximab. Twelve months post-rituximab, 75% of patients had either partial or complete remission.7

A case of recurrent immunotactoid glomerulopathy after transplantation, a glomerular disorder typified by hollow cylindrical and sometimes spherical micotubular deposits, has been reported to respond to rituximab with reduction and stabilization of serum creatinine level but with persistent proteinuria.111 From the point of adverse events, rituximab is generally well-tolerated. Most of the reported side effects have been typically mild, transient and felt to be due to infusion reaction. However, a number of recent case reports and studies have raised concerns regarding potential complications of rituximab usage in transplant setting. Although the rate of infection was similarly high in both groups (45.5% rituximab-treated vs. 53.9% controls), the mortality rate was significantly higher in the rituximab group (9.1% vs. 1.6%).111,112 Others have reported cases of late-onset Pneumocystis jiroveci pneumonia, cryptogenic organizing
pneumonia and JC virus associated progressive multifocal leukoencephalopathy in patients treated with rituximab in post-transplant period.\textsuperscript{3,3,33,14}

**Conclusions**

As one of a newer class of immune modulating and immunosuppressive agents, i.e., antibody-based therapeutics, rituximab offers an important option for treatment of refractory and relapsing glomerular diseases. However, systematic review has shown that its use is still at an early stage (Table 1). Rituximab has been effective in PLA\textsubscript{2}-associated membranous glomerulonephritis, but has not been uniformly effective in inducing remission in lupus nephritis and other glomerular diseases, highlighting the multiplicity of mechanisms involved in glomerular diseases. Mechanisms of glomerular diseases include damage to an essentially impermeable glomerular barrier; alterations in the charge and size selectivity of glomerular permeability; dysfunction of retrieval pathway of filtered protein by tubular cells; podocyte injury associated with disruption of signaling from any of the podocyte’s specialized membrane domains, including slit diaphragm, apical and basal membranes, or originating at the level of the actin cytoskeleton; and single-gene defects. TRPC6 encoding gene, a non-selective cation channel of the TRP family expressed in podocyte foot processes, APO\textsubscript{L1} (apolipoprotein L-1) and MHY9 (non-muscle myosin heavy chain 9 gene have been linked with glomerular diseases. Mutations in nephrin, podocin and \(\alpha\)-actinin-4 gene alleles have been demonstrated to lead to congenital nephrosis. Cytokine overproduction, T cell and B cell activation, defective T-regulatory functions, circulating auto-antibodies interacting with antigens native to or planted in the glomerular capillary wall at the podocyte cell membrane-basement membrane interface are also involved. It is therefore not surprising that one agent is not suitable for all in the treatment of glomerular diseases. The role of rituximab in the treatment of glomerular diseases continues to expand with renewed understanding of the pathomechanism of the diseases involved. Finally, the potential complications associated with this agent dictate that rituximab use in renal diseases must be further elucidated through larger-scale randomized trials that compare rituximab with current gold standard treatments.

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**Table 1. Proposed role of rituximab in glomerular diseases**

| Glomerular Disease                  | Proposed Role of Rituximab |
|------------------------------------|----------------------------|
| Lupus nephritis                    | Induction of remission     |
| Relapsing or refractory disease    | Combination therapy with cyclophosphamide for induction of remission |
| ANCA-associated vasculitides       | Poor response in granulomatosis manifestations (orbital/pachymeningitis) |
| Cryoglobulinemic vasculitis        | Induction of remission     |
| Hepatitis C-related               |                            |
| Non-Hepatitis C-related           |                            |
| Non-cryoglobulinemic glomerulonephritis |                            |
| Idiopathic membranous nephropathy |                            |
| Anti-PLA\textsubscript{2} -related diseases |                            |
| Overcome dependency on calcineurin inhibitors |                            |
| Autoimmune thrombotic thrombocytopenic purpura | Induction of remission |
| Focal segmental glomerulosclerosis | Recurrent FSGS in transplanted kidney |
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