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REVIEW ARTICLE

Rituximab in kidney disease and transplant

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Abstract

Rituximab is a chimeric monoclonal antibody that binds to CD20 antigen of B-cells. It depletes the level of mature B-cells by various mechanisms such as mediation of antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and B-cell apoptosis. Rituximab is a USFDA approved drug for clinical use in non-Hodgkin's B-cell lymphoma (NHL), rheumatoid arthritis, chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis and pemphigus vulgaris. It is also known for its "off label" use in renal disease and renal transplant worldwide. However, the exact mechanisms by which it exerts its effect in the aforementioned condition remain unclear but may be related to its long-term effects on plasma cell development and the impact on B-cell modulation of T cell responses. This review discusses the current use of rituximab in renal disease and renal transplantation, and its potential role in novel therapeutic protocols.

KEYWORDS
renal diseases, renal transplant, rituximab

1 | INTRODUCTION

Rituximab is a chimeric murine/human monoclonal IgG1 kappa monoclonal antibody that binds to the CD20 antigen present on the cell surface.[1] It is a product consisting of approximately 20% mouse and 80% human protein and was the first monoclonal antibody to be approved for clinical use in the therapy of cancer patients suffering from lymphoma. It is approved for use against indolent B-cell non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA) in patients with an incomplete response or intolerance to tumor necrosis inhibitors (TNFi), granulomatosis with polyangiitis and microscopic polyangiitis.[2,3] Recently rituximab has been approved by the USFDA for pemphigus vulgaris.[4]

CD20, an activated-glycosylated phosphoprotein, is an antigen expressed on the surface of B-cells in pre-B-cell and mature phases. Rituximab depletes mature B-cells and pre-B-cells through memory B-cell stages only if this trans-membrane antigenic protein is present. It doesn't deplete stem cells, pro-B-cells, terminally differentiated plasma cells, and plasmablasts because these cells do not express CD20 on their surfaces.[5] Rituximab depletes B-cells by various mechanisms, including mediation of antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and B-cell apoptosis.[6] It has been shown to be efficacious in clinical trials of patients with RA and hematological malignancies, with a reasonable safety profile and a small risk of serious infectious events. Treatment effects were stable over time and repeated courses. Other opportunistic infections were rare with the treatment.[7,8]

Antibody production is a characteristic and pathological marker for number of systemic diseases. It may affect the kidneys and may lead to serious problems in renal transplantation. Rituximab is known for its "off label" use for the treatment of various disorders, but the exact mechanism by which it exerts its effect remains unclear. It is used to treat systemic lupus erythematous,[9] membranous nephropathy,[10] mixed essential cryoglobulinemia,[11] focal segmental glomerulosclerosis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis[12] and hemolytic uremic syndrome,[13] specifically in cases which are resistant to conventional therapy. In transplantation, it is used in induction/desensitization in refractory-B-cell-associated or antibody-associated rejection.[14] Herein, we review the latest reports on the use

of rituximab in kidney disease and transplantation. Randomized controlled trials are warranted for several of the indications discussed below, to confirm or refute the benefits reported to date.

2 | SYSTEMIC LUPUS ERYTHEMATOSUS

Lupus nephritis is a major cause of mortality and morbidity in patients with SLE,[15] with renal involvement occurring in up to two-thirds of patients. B-cells are thought to play a crucial role in the pathogenesis of SLE, including the production of autoantibodies, the regulation of T-cell activation, and the production of cytokines involved in the disease;[16] therefore, rituximab would seem a logical therapeutic choice in SLE. Ruth et al reported in a prospectively monitored cohort of 18 patients, who were on steroids prior to the development of lupus nephritis, treated with rituximab induction therapy (two 1 g doses of rituximab, given on days 1 and 15) and mycophenolate mofetil (MMF) maintenance therapy (1 g/d). Seventy-eight per cent of patients achieved a complete response (CR) or partial remission (PR), with a sustained response of 12/18 (67%) at 1 year. Proteinuria significantly decreased from a mean protein:creatinine ratio (PCR) of 325 mg/mmol to 132 mg/mmol at 1 year ($P = 0.004$). There was a significant increase in serum albumin from a mean of 29-34 g/L at 1 year ($P = 0.001$). No severe infections were reported. Six patients stopped prednisolone, and 6 patients reduced their maintenance dose.[17]

Borja Gracia-Tello et al reported that early treatment of SLE patients with rituximab was safe and effective, and enabled a reduction in steroid use. Sixteen female patients with SLE were treated at or shortly after diagnosis with rituximab (1 g on days 1 and 14). All patients given rituximab achieved B-cell depletion. The mean number of flares during follow-up was 2.63 in the rituximab group and 4 in the controls (NS, $P = 0.14$). After treatment with rituximab, mean anti-dsDNA antibody level fell from 1114 to 194 U/mL at 18 months ($P = 0.043$), mean serum erythrocyte sedimentation rate (ESR) fell by > 70% at 6 months and was maintained during follow-up, and serum complement (C3) level normalised in eight patients. The mean cumulative prednisolone dose at 60 months for the patients who were given rituximab (n = 11) was 4745.67 mg vs 12 553.92 mg for the controls ($P = 0.01$).[18]

3 | IDIOPATHIC MEMBRANOUS NEPHROPATHY

Membranous nephropathy (MN) remains a leading cause of nephrotic syndrome in adults. In most patients, an underlying etiology for the lesion is unknown and the disorder is termed idiopathic.[19,20]

The M-type phospholipase A2 receptor (PLA2R), a transmembrane protein expressed on glomerular podocytes, has been demonstrated to be the target antigen in most cases of idiopathic MN (IMN).[21] This creates a paradigm whereby circulating autoantibodies to PLA2R form in situ immune complexes at the level of the podocyte, leading to the development of MN. The central mechanistic role for autoantibodies in MN has provided a rationale for B-cell targeted therapy.[22] Remuzzi et al used rituximab successfully in eight patients who had idiopathic membranous nephropathy with persistent nephrotic syndrome. Four weekly infusions of rituximab (375 mg/m^2) were given. At the end of weeks 4 and 20, urinary protein decreased from a mean (SE) of 8.6 g/24 h (1.4) to 3.8 (0.8) and 3.7 (0.9), respectively ($P < 0.0001$). At week 20, albuminuria and albumin fractional clearance decreased by 70% and 65%, and serum albumin increased by 31%. CD20 B lymphocytes also fell below normal ranges up to study end.[23]

Marco et al confirmed that treatment with rituximab (in 13 patients as first-line therapy, in the remaining 25 after conventional immunosuppressive therapy) was remarkably safe and allowed for a large percentage of complete or partial remissions in 38 patients with MN. Patients were given four weekly intravenous infusions of rituximab at a dose of 375 mg/m^2, and 39.5% (15 patients), 36.8% (14 patients) and 76.3% (29 patients) achieved complete remission, partial remission and the composite endpoint (complete or partial remission), respectively. The 24-h proteinuria level was reduced significantly, while albuminemia increased constantly. Renal function did not significantly change during the observation period. Circulating CD19$^+$ B-cells were reduced significantly from the baseline value to the 24-month value ($P < 0.01$).[24] Clinical outcomes of IMN patients treated with rituximab are summarized in Table 1.

4 | MIXED ESSENTIAL CRYOGLOBULINEMIA

Mixed cryoglobulinemia is a systemic vasculitis, primarily mediated by immune complexes and is associated with hepatitis C virus (HCV) infection and B-cell lymphoproliferation.[25] Rituximab has the potential to deplete the expanded population of B-cells developing in HCV-associated vasculitis thereby reducing the formation of the cryoglobulin immune complex.[26] In a prospective randomized controlled trial, Sneller et al treated 24 HCV-associated cryoglobulinemic patients with rituximab (375 mg/m^2 per week for 4 weeks). Eighty-three per cent of patients achieved remission compared with one patient in the control group (8%), a result that met the criterion for stopping the study ($P < 0.001$). No adverse effect of rituximab on HCV plasma viremia or hepatic transaminase levels was observed.[27]

In a long-term, prospective, randomized controlled trial, De Vita et al reported that rituximab monotherapy represents a very good option for severe cryoglobulinemic vasculitis and can be maintained over the long term in most patients. Fifty-nine patients were randomized to nonrituximab (RTX) or RTX groups (two infusions of 1 g each). Survival of treatment at 12 months, the primary end point, was statistically higher in the RTX group (64.3% vs 3.5%; $P < 0.0001$), as well as at 3 months (92.9% vs 13.8%; $P < 0.0001$), 6 months (71.4% vs 3.5%; $P < 0.0001$), and 24 months (60.7% vs 3.5%; $P < 0.0001$). The Birmingham Vasculitis Activity Score decreased only after treatment with rituximab (11.9 ± 5.4

TABLE 1 Rituximab in idiopathic membranous nephropathy

Reference	Study	Dose of rituximab	Patients, N	Outcome
Fiorentino et al[24]	Prospective observational study	375 mg/m^2, 4-weekly IV infusions	38	39.5% CR 36.8% PR 76.3% CR or PR Decreased proteinuria Increased albuminemia Decrease in circulating CD19$^+$ B-cells
Ruggenenti et al[55]	Prospective observational study	375 mg/m^2, 4 weekly IV infusions	8	Decreased proteinuria Increased serum albumin concentration Renal function stabilized
Fernando et al[56]	Prospective study	375 mg/m^2, 4 weekly IV infusions	20	Decreased proteinuria Increased creatinine clearance CR in 4 patients PR in 12 patients
Busch et al[57]	Prospective single center study	375 mg/m^2, 4 weekly IV infusions	14	Decreased proteinuria CR in 3 patients PR in 12 patients
Ruggenenti et al[58]	Prospective observational study	375 mg/m^2, 4 weekly IV infusions	100	65 patients achieved CR or PR Increased serum albumin Decreased proteinuria
Cravedi et al[59]	Prospective, matched-cohort study	375 mg/m^2, 4 weekly IV infusions	11	Decreased proteinuria 8 patients and 7 reference patients achieved full (3 vs 2) or partial (5 per cohort) proteinuria remission

CR, complete remission; PR, partial remission.

at baseline to 7.1 ± 5.7 at month 2; $P < 0.001$) up to month 24 (4.4 ± 4.6; $P < 0.0001$). Overall, rituximab treatment was well tolerated.[11]

5 | FOCAL SEGMENTAL GLOMERULOSCLEROSIS

The treatment of idiopathic steroid-resistant FSGS remains a worrying challenge for nephrologists. The potential usefulness of rituximab has also been explored in patients with steroid-dependent or steroid-resistant forms of nephrotic syndrome.[28] In a multicenter retrospective study by Garrouste et al, 19 patients who developed FSGS recurrence at 12 (1.5-27) days post transplantation were treated with rituximab (375 mg/m^2, a median of 2 (1-4) infusions). Nine of 19 had complete remissions and 3 of 19 had partial remissions. Estimated glomerular filtration rates were significantly higher in the responding patients than in nonresponding patients at month (M)12, M36, and M60. Kidney survival at 5 years was 77.4%. The 5-year graft survival rates in the responding patients and the nonresponding patients were 100% and 36.5%, respectively ($P = 0.01$).[29] Fornoni et al treated 27 out of 41 patients with rituximab (375 mg/m^2, single dose) at high risk of recurrent FSGS at the time of kidney transplant. Their study suggested that treatment of high-risk patients with rituximab at the time of kidney transplant might prevent recurrent FSGS by modulating podocyte function in an SMPDL-3b-dependent manner.[30]

6 | ANTINEUTROPHIL CYTOPLASMIC ANTIBODY

Microscopic polyangiitis and Wegener's granulomatosis are classified as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, as most patients with generalized disease have antibodies against proteinase 3 or myeloperoxidase. The ANCA-associated vasculitides affect small-to-medium-size blood vessels, with an inclination for the respiratory tract and kidneys. In ANCA-associated vasculitis, the percentage of activated peripheral-blood B lymphocytes correlates with disease activity. Studies suggest that rituximab has shown promise as a remission-induction agent in ANCA-associated vasculitis by depleting B-cells.[31,32] In a multicenter, randomized, double-blind, double-dummy, noninferiority trial by Stone et al, rituximab therapy was found to be more effective than daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis. A total of 197 ANCA-positive patients were randomized to receive rituximab in cyclophosphamide. Primary end point was achieved by 64% of patients in the rituximab group compared to 53% of patients in cyclophosphamide group. The rituximab-based regimen was more efficacious than the cyclophosphamide-based regimen for inducing remission of relapsing disease (67% vs 42%). Rituximab was also as effective as cyclophosphamide in the treatment of patients with major renal disease or alveolar hemorrhage. No significant differences between the treatment groups with respect to rates of adverse events was observed.[33]

In a single-center cohort study by McAdoo et al of 66 patients with renal anti-neutrophil cytoplasm antibody-associated, a combined regimen of rituximab and cyclophosphamide proved to be potentially superior to current standards of care. Sixty-six patients were treated with a combination of oral corticosteroids, rituximab and low-dose pulsed intravenous cyclophosphamide, followed by a maintenance regimen of azathioprine and tapered steroid for the treatment of biopsy-proven renal involvement in AAV. Ninety-four per cent of patients achieved disease remission by 6 months. Patient and renal survival were 84% and 95%, respectively, at 5 years. Eighty-four per cent achieved ANCA-negative status and 57% remained B-cell deplete at 2 years, with low rates of major relapse. The serious infection rate during long-term follow-up was 1.24 per 10 patient-years. Treatment with this regimen was associated with a reduced risk of death, progression to end-stage renal disease, and relapse, compared with propensity-matched patients enrolled in EUVAS trials.[34]

7 | HAEMOLYTIC URAEMIC SYNDROME

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterized by thrombocytopenia, microangiopathic haemolytic anaemia, neurological and renal abnormalities and fever. Since such criteria do not distinguish TTP from haemolytic uraemic syndrome (HUS), the comprehensive term TTP-HUS is more appropriate.[35,36] Rituximab is reportedly effective in TTP-HUS patients with or without antibody-mediated ADAMTS-13 deficiency, as well as in cases of refractory/relapsing cases.[37-39] In 4 cases reported by Caramazza et al, patients with relapsed or refractory HUS received rituximab initiated as a single agent once a week for 4 weeks, at a dose of 375 mg/m^2. All four patients achieved clinical remission and rituximab was well tolerated.[40] Kameda et al reported two cases of refractory thrombotic thrombocytopenic purpura associated with collagen vascular disease. After both patients received two doses of intravenous rituximab (375 mg/m^2 once per week), hemoglobin level and platelet counts were gradually elevated and fragmented red blood cells disappeared.[38]

8 | RITUXIMAB IN RENAL TRANSPLANTATION

Rituximab is widely used in ABO blood group incompatible transplantation. It is also an effective treatment for post-transplant lymphoproliferative disorder, and is used in both human leukocyte antigen (HLA) antibody incompatible renal transplantation and the treatment of acute rejection.

Historically, ABO-incompatible (ABOi) kidney transplantations have only been undertaken after splenectomy and unspecific plasmapheresis and with quadruple drug immunosuppression plus B-cell specific drugs. The first description of use of rituximab to replace splenectomy as a desensitization treatment in ABOi renal transplantation came from Stockholm in 2003. A protocol with a 10-day pretransplant conditioning period, starting with single dose of rituximab (375 mg/m^2), followed by full dose tacrolimus, mycophenolate mofetil, and prednisolone, followed by antigen-specific immunoadsorption, was used in four patients. The ABO-antibodies were readily removed by the antigen-specific immunoadsorption and were kept at a low level post transplantation by further adsorptions. There were no side effects, and all patients have normal renal-transplant function.[41]

In another study by Tydén and colleagues, one dose of rituximab (375 mg/m^2), was given 10 days prior to transplant to 12 patients, together with other immunosuppressants. Postoperatively, a standard triple-drug immunosuppressive protocol was followed, together with an immunosorbent. In the patient with the longest follow-up (almost 3 years), the CD20-positive cells were not detectable until 12 months posttransplantation. No side effects related to rituximab were observed and there were no serious infections.[42] Recently Honda et al retrospectively compared 29 pediatric ABOi living donor liver transplantation (LDLT) recipients with 131 non-ABOi LDLT recipients. There were no significant differences in the incidence of infection, vascular complications, biliary complications, and acute cellular rejection between the ABOi and non-ABOi group. The cumulative graft survival rates at 1, 3, and 5 years for the non-ABOi group were 92.1%, 87.0%, and 86.1%, and those for ABOi group were 82.8%, 82.8%, and 78.2%, respectively. They concluded that ABOi LDLT is a feasible option for pediatric end-stage liver disease patients.[43] The allograft survival and patient survival rates for published reports of ABOi renal transplantation using rituximab are summarized in Table 2.

In HLA antibody incompatible renal transplants, rituximab is often given at the time of transplantation or even post transplant.[44,45] Jackson et al examined post-transplant HLA antibody levels in 25 recipients desensitized with rituximab induction and 25 without, to determine the impact of B-cell depletion. They found significantly less HLA antibody rebound in the rituximab-treated patients (7% of donor specific antibodies (DSAs) and 33% of non-DSAs) compared to a control cohort desensitized and transplanted without rituximab (32% DSAs and 55% non-DSAs). Also, the magnitude of the increase was significantly larger among patients who did not receive rituximab. Compared to controls, rituximab-treated patients had a significantly greater mean reduction in DSA (−2505 vs −292 mean fluorescence intensity), but a similar rate of DSA persistence (52% in rituximab treated and 40% in nontreated recipients). They inferred that rituximab induction in HLA incompatible recipients reduced the incidence and magnitude of HLA antibody rebound, without affecting DSA elimination, or antibody mediated rejection.[46]

Use of rituximab as a treatment for acute renal allograft rejection has been purely descriptive, mainly single-case reports or case series.[47] In a randomized controlled trial, Zarkhin et al reported 1-year outcomes of rituximab vs standard-of-care immunosuppression for treatment of biopsy confirmed, acute transplant rejection with B-cell infiltrates, in 20 consecutive recipients (2-23 years). Rituximab was administered by intravenous infusion at a standard dose of 375 mg/m^2 weekly for four consecutive weeks. Complete tissue B-cell depletion and rapid peripheral B-cell depletion was observed. Peripheral CD19 cells recovered at a mean time of approximately 12 months. Some benefits in recovery

TABLE 2 Results from adult ABOi renal transplant programs using rituximab

Authors	Number of patients	Dose of rituximab	Follow-up	Outcome
Sonnenday et al[60]	6	375 mg/m^2, single dose	12 mo	Mean SCR. was 1.3 ± 0.1 mg/dL No episodes of AMR Stable allograft function
Genberg et al[61]	15	375 mg/m^2, single dose	3 y	100% patient survival 87% overall graft survival Acute rejection in 1 patient
Sivakumaran et al[62]	10	375 mg/m^2, single dose	1 y	100% patient survival Mean SCr = 1.45 ± 1.04 mg/dL 4 episodes of AMR 2 incidents of DGF
Genberg et al[63]	43	375 mg/m^2, single dose	4.5 y	93% overall patient survival 91% graft survival 9.3% incidence of AMR
Melexopoulou et al[64]	30	375 mg/m^2, single dose	6 y	92% patient survival 81% graft survival No CAMR 13.3% ACR
Jha et al[65]	20	200 mg, single dose		90% patient survival 95% graft survival 15% AMR
Lee et al[66]	59	375 mg/m^2, or 200 mg single dose	2 y	95.8% patient survival 94.9% graft survival 15.3% AMR 1 graft loss
Kong et al[67]	79	53% patients mean 644 ± 226 mg/body47% patients 203 ± 14 mg/body	21 mo	99.2% patient survival 97.5% graft survival 14% patients had acute rejection
Rostaing et al[68]	12	375 mg/m^2, two dose	19 mo	91.6% graft survival 100% patient survival 3 patient had CAMR 58.3% showed nearly normal kidney biopsy
Ray et al[69]	45	200 mg/body single infusion	370 d	Mean SCr = 1.21 mg% 97.78% graft survival 97.78% patient survival

ACR, acute cellular rejection; AMR, antibody-mediated rejection; CAMR, chronic antibody-mediated rejection; DGF, delayed graft function; SCR, serum creatinine.

of graft function ($P = 0.026$) and improvement of biopsy rejection scores at both the 1- ($P = 0.0003$) and 6-month ($P < 0.0001$) follow-up biopsies were observed. Reappearance of C4d deposition was absent in follow-up biopsies after rituximab therapy, but was present in 30% of control patients. There was no change in DSA in either group, independent of rejection resolution.[48]

A few clinical studies have shown improvement in the treatment of chronic active antibody-mediated rejection (CAMR) following the administration of rituximab in combination with other therapies in some patients.[49] Hong et al administered a single dose of rituximab (375 mg/m^2) together with intravenous immunoglobulin (IVIg) in six renal transplant recipients who showed progressive deterioration in graft function and CAMR as diagnosed by biopsy. After the treatment, allograft function improved or stabilized in 3 patients in the responder group. The amount of proteinuria also decreased in the responder group, suggesting that the combination of rituximab and IVIg was effective in early-stage CAMR.[50]

The term PTLD encompasses a heterogeneous group of lymphoproliferative disorders that may occur after transplantation of solid organs and hematopoietic cells.[51] PTLD has been reported in 1% of

renal transplant recipients.[52] Rituximab has been demonstrated to be an effective treatment for PTLD.[53] In a retrospective study of eight patients with PTLD, Nieto-Rios et al concluded that the disorder can be managed successfully, with reduction of immunosuppression, conversion to m-TOR, and rituximab-based schemes. The first-line therapy consisted of rituximab given as a 375 mg/m^2 intravenous infusion for 4 hours, weekly. The overall response rate was 87.5% (62.5% complete response, 25% partial response). Survival was 87.5%, with a median follow-up of 34 months.[54]

9 | CONCLUSION

Emerging evidence suggests that rituximab may be an effective and safe treatment in renal disorders and renal transplant. However, ideal dosing strategies and combination with other agents is still debatable. Studies designed to answer these questions should delineate the best use of rituximab in nephrology, and randomized controlled trials are clearly required before accepting rituximab as a standard treatment.

CONFLICT OF INTEREST

None.

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