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REVIEW

Rituximab use in adult primary glomerulopathy: where is the evidence?

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Abstract: Rituximab is a chimeric anti-CD20 antibody that results in depletion of B-cell lymphocytes. It is currently used in the treatment of a variety of autoimmune diseases, in addition to CD20-positive lymphomas. The use of rituximab in the treatment of the adult primary glomerular diseases has emerged recently, although not yet established as first-line therapy in international guidelines. In patients with steroid-dependent minimal change disease or frequently relapsing disease, and in patients with idiopathic membranous nephropathy (IMN), several retrospective and prospective studies support the use of rituximab to induce remission, whereas in idiopathic focal and segmental glomerulosclerosis (FSGS), the use of rituximab has resulted in variable results. Evidence is still lacking for the use of rituximab in patients with immunoglobulin A nephropathy (IgAN) and idiopathic membranoproliferative glomerulonephritis (MPGN), as only few reports used rituximab in these two entities. Randomized controlled trials (RCTs) are warranted and clearly needed to establish the definitive role of rituximab in the management of steroid-dependent and frequently relapsing minimal change disease, IMN, both as first-line and second-line treatment, and in MPGN. We await the results of an ongoing RCT of rituximab use in IgAN. Although current evidence for the use of rituximab in patients with idiopathic FSGS is poor, more RCTs are needed to clarify its role, if any, in the management of steroid-resistant or steroid-dependent FSGS.

Keywords: rituximab therapy, primary glomerulopathy, adult glomerunephritis, membranous nephropathy, minimal change disease, focal and segmental glomerulosclerosis, immunoglobulin A nephropathy, idiopathic membranoproliferative glomerulonephritis

Introduction

Rituximab is a chimeric monoclonal antibody (murine/human), designed to bind specifically to the CD20 receptor – lymphocyte differentiation antigen B – present in the cell membrane of pre-B-cells and mature B but not in the plasma cells. The binding of rituximab to CD20 causes a depletion of B lymphocytes through three mechanisms: antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.[1]

Rituximab is currently approved for the treatment of CD20-positive lymphoma and rheumatoid arthritis; however, it is increasingly being used off-label in a wide variety of autoimmune disorders.[2]

In this review, we will focus on the role of rituximab in the management of adult patients with primary glomerular disease. We will emphasize on the pathophysiological aspects and recent clinical trials supporting the use of rituximab in the management of minimal change disease (MCD), idiopathic membranous nephropathy (IMN), and primary focal and segmental glomerulosclerosis (FSGS), immunoglobulin A

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nephropathy (IgAN), and idiopathic membranoproliferative glomerulonephritis (MPGN).

For this review we searched MEDLINE and PubMed for reviews, case reports, case series, retrospective, and prospective studies, using keywords such as "Rituximab", "Therapy", "glomerulonephritis", "minimal change disease", "focal and segmental glomerulosclerosis", "idiopathic membranous nephropathy", "IgA nephropathy", and "membranoproliferative glomerulonephritis". We included some of the yielded case reports; however, we tried to include all relevant retrospective and prospective studies published to date, testing the use of rituximab in these pathologies. In addition, we searched the clinical trial registry ClinicalTrials.gov for ongoing trials related to our review.

Rituximab in MCD

MCD accounts for up to 20% of cases of nephrotic syndrome in the adult population.[3] Although most of the patients with nephrotic syndrome related to MCD will respond to corticosteroid therapy, up to a third will become corticosteroid-dependent or have a frequently relapsing disease.

For this subset of patients, current guidelines suggest using other regimens such as oral cyclophosphamide, calcineurin inhibitors (CNIs) (tacrolimus or cyclosporine), or mycophenolate mofetil (MMF) in patients who are intolerant to the abovementioned agents. These guidelines noted the need for randomized clinical trials to establish the role of rituximab in this setting.[4]

Historically, MCD has been considered a lymphocyte T-cell pathology. However, recent advances in our understanding of the pathways involved in the pathogenesis of the disease identified a more complex pathogenesis with participation of innate immunity, B-cells, and regulatory T-cells.[5]

Moreover, it has been shown that rituximab binds to the sphingomyelin phosphodiesterase acid-like 3b protein in glomerular podocytes and regulates acid sphingomyelinase activity, stabilizing the actin cytoskeleton, and preventing apoptosis of podocytes, thus providing another rationale for the use of rituximab in the management of MCD.[6]

The first case that reported the use of rituximab in the management of MCD in adults was in 2007. In this report, a patient with a multirelapsing nephrotic syndrome secondary to MCD (>30 relapses), who failed treatment with all other potentially steroid-sparing drugs including cyclophosphamide, cyclosporine, and MMF, was treated with rituximab at 375 mg/m^2 every week for 4 weeks. Long-term remission was achieved starting 3 weeks after therapy, and was still maintained after 28 months at the time of writing of the report.[7] Since the publications of this report, several other case reports of the successful use of rituximab in the setting of frequent relapses/steroids dependence were published.[8]

Following these case reports, several retrospective and prospective trials have been published.

In one retrospective case series, 17 patients with steroid-dependent or frequently relapsing MCD despite several immunosuppressive therapy were treated with rituximab and analyzed. The infusion protocol for rituximab differed between patients, and some of the patients received a second course of rituximab during follow-up because of CD19 cell recovery. Rituximab achieved a sustained response with no relapse in 65% of patients after 2 years. No infectious or hematologic complications were observed during follow-up.[9]

In another retrospective analysis involving 41 patients with steroid-dependent or multiple relapsing MCD, rituximab achieved complete clinical response (defined as urine protein over creatinine ratio [UPCR] of <0.3 g/g and withdrawal of all immunosuppressive treatment) in 61% of patients, and a partial clinical response in 17% (defined as UPCR of <0.3 g/g and withdrawal of at least one immunosuppressive drug). Twenty-two percent of patients did not respond to rituximab therapy. No serious adverse events were noted secondary to rituximab treatment.[10]

In a prospective trial involving 25 patients with steroid-dependent MCD, rituximab was administered twice at 6 months interval, at a dose of 375 mg/m^2. All patients were on prednisolone, 20 patients were on cyclosporine A, three patients were on MMF, and five patients were on mizoribine. Twelve months after the first rituximab infusion, only four patients out of 25 relapsed, only four patients remained on prednisolone, and only six patients remained on cyclosporine. Furthermore, the mean doses of both prednisolone and cyclosporine A were reduced significantly from 26.4±11.5 mg/day at baseline to 1.1±2.8 mg/day at 12 months for prednisolone and from 110±43 mg/day at baseline to 30±48 mg/day at 12 months for cyclosporine A. Most of the relapses developed simultaneously with the recovery of the B-cell count (CD19 or CD20), supporting that suppression of B-cell is involved in the pathophysiology of MCD.[11]

In an extended prospective follow-up of the previous trial to evaluate the long-term effects of rituximab, infusions of rituximab at 375 mg/m^2 were continued at 6 months interval for 24 months. The cohort was then divided into a treatment continuation group (20 patients), in whom rituximab infusions were maintained at 6 months intervals beyond the initial four doses, and treatment discontinuation group (five patients), in whom rituximab therapy was stopped after the initial four

doses. Complete remission (urine protein <0.3 g/day) was maintained in all 20 patients of the continuation therapy group, from 36 to 54 months after the first rituximab infusion. Only one patient out of the five of the discontinuation therapy group developed relapse requiring resumption of rituximab infusions. Interestingly, and despite B-cell repletion, ten patients with B-cell repletion (including four from the treatment discontinuation group and six from the treatment continuation group) maintained complete remission, suggesting that single infusion protocols of rituximab may be an effective and safe treatment regimen for patients with steroid-dependent MCD, and that B-cell repletion does not always correlate with disease relapse.[12]

In summary, current evidence supports the use of rituximab in steroid-dependent and frequently relapsing MCD; however, properly designed randomized controlled trials (RCTs) are needed to establish the superiority and safety of rituximab as compared to other currently used agents in this setting, such as cyclophosphamide, cyclosporine, and MMF. Table 1 summarizes the characteristics of the discussed studies of rituximab in MCD.

Rituximab in IMN

Membranous nephropathy is considered to be the most common cause of nephrotic syndrome in adults.[13] Seventy percent of cases are labeled as primary or idiopathic.[14] Spontaneous remission develops in 30%–50% of patients with IMN and nephrotic syndrome.[15] Thus, immunosuppressive therapy is reserved only for cases with high risk of progression.[16] Currently recommended first-line immunosuppressive agents, such as steroids and cyclophosphamide, are not free of harm. Serious complications like bone marrow suppression, infection, iatrogenic diabetes, infertility, and malignancy, can occur.[17]

In the light of the recent discovery of autoantibodies against the podocyte enzyme, M-type phospholipase A_2 receptor (PLA2R), our understanding of the pathogenesis of IMN has improved dramatically.[18] These autoantibodies are present in most patients with IMN. Antibodies to other podocyte antigens, thrombospondin type 1 domain containing protein 7 may be present as well.[19] Accordingly, this major breakthrough heightened the value of the B-cell depleting agent rituximab as an attractive therapeutic option.

In fact, in a cohort of 35 patients with IMN, 71% (25/35) had positive anti-PLA2R antibodies (PLA2R-Ab) and they declined or disappeared in 68% (17/25) within 12 months after rituximab therapy. Decline in the autoantibody levels was translated into a higher rate of remission of proteinuria.[20]

Most of the current literature on the use of rituximab in IMN comes from observational studies and one recently published RCT.

The earliest report was published in 2002 by Remuzzi et al. In this study, four weekly doses of rituximab (375 mg/m^2) were given to eight patients with IMN who had nephrotic range proteinuria (>3.5 g/24 h) for at least 6 months without remission, despite full-dose angiotensin-converting-enzyme inhibitors (ACEI). Mean proteinuria decreased from 8.6 g to 3.8 g/24 h during the treatment period. Two patients achieved complete remission (proteinuria <1 g/24 h), and three patients achieved partial remission.[21]

A different rituximab regimen was employed in a prospective observational study in 15 severely nephrotic patients (urine protein excretion range between 6.1 and 23.5 g/24 h) refractory to maximally tolerated doses of ACEIs and/or angiotensin receptor blockers (ARBs) for at least 6 months. Patients received two infusions of rituximab at a dose of 1 g on days 1 and 15. Those who remained with significant proteinuria (>3 g/24 h) at 6 months, and had recovered B-cell counts were given a second course of the same treatment (ten patients). Mean proteinuria decreased from 13±5.7 to 6±7.3 g/24 h at 12 months. Furthermore, there was a 60% complete and partial remission rate at 1 year.[22]

In a nonrandomized study, Ruggenenti et al prospectively monitored the outcomes of 100 consecutive patients with IMN treated with 4 weekly rituximab infusion. Duration of follow-up was at least 6 months. Thirty-two patients had already been treated at other institutions with steroids alone or in combination with alkylating agents, CNIs, or other immunosuppressant. Twenty patients (60%) had transient partial remissions. Nevertheless, no patient was in complete or partial remission after completion of the last course of immunosuppression and no one had any complete or partial remission on subsequent follow-up. At baseline evaluation, median serum creatinine was 1.2 mg/dL, median serum albumin was 2.2±0.6 g/dL, and median proteinuria was 9.1 g/24 h. Median duration of proteinuria before rituximab administration was 25.5 and 65.4 months for the 32 patients with second-line therapy. Blood pressure was well controlled and all patients were on ACEIs. Over a median follow-up of 29 months after rituximab administration, 65 patients achieved complete or partial remission. The median time to remission was 7.1 months. Similar proportion of patients achieved complete or partial remission among those given rituximab as first-line (47 of 68) or second-line (18 of 32) therapy. Rituximab was well tolerated and there was no treatment-related adverse events apart from some reactions to the first infusion.[23]

Table 1 Characteristics of discussed studies of rituximab in MCD

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Munyentwali et al[9]	Retrospective case series	17 patients with steroid-dependent or frequently relapsing MCD	Variable: 15 patients with 1–4 weekly infusions at 375 mg/m^2	Response to rituximab and relapses	65% of patients did not relapse (mean f/u of 26.7 months)
			Two patients with 1 g on days 1 and 15	Reduction of IS treatments	70% of patients achieved withdrawal of steroids and other drugs after 12 months
			Patients received additional doses of rituximab if CD19 recovery	Adverse events	No hematological or infectious complications during follow-up
Guitard et al[10]	Retrospective chart review	41 patients with steroid-dependent or frequently relapsing MCD	Variable: 21 patients received 1 g on days 1 and 15	Complete clinical response: CR (UPCR <0.3 g/g) + withdrawal of all IS treatments	61% of patients achieved complete clinical response
		51% with nephrotic syndrome	12 patients received 4 weekly infusions (375 mg/m^2)	Partial clinical response: CR + withdrawal of at least one IS drug	17% of patients achieved partial clinical response
			One received 1 g once	Side effects	No serious adverse events during follow-up
			Five received 2 weekly infusions of 375 mg/m^2		
			Two received 3 weekly infusions of 375 mg/m^2		
Takei et al[11]	Prospective, cohort study, with historical controls	25 patients with steroid-dependent and frequently relapsing MCD	375 mg/m^2 twice at an interval of 6 months	Patients with relapse 12 months after rituximab as compared to 12 months before rituximab therapy	4/25 patients relapsed, as compared to 25/25 patients before rituximab
				Side effects	Mild infusion reactions in three patients, one exanthema, and one leukopenia
Iwabuchi et al[12] (follow-up of Takei et al[11])	Prospective, cohort study, with historical controls	25 patients with steroid-dependent and frequently relapsing MCD	375 mg/m^2 every 6 months for 24 months	Number of relapses before and after rituximab therapy	108 episodes of relapse in the 24 months before rituximab, and eight episodes during the 24 months after
			After 24 months, 20 patients continued rituximab every 6 months (treatment continuation group), and five patients discontinued rituximab (treatment discontinuation group)	CR: urine protein excretion of <0.3 g/day	CR maintained in all patients at 24 months 1/5 of treatment discontinuation group developed relapse at 8 months after last rituximab infusion
				Side effects	No hematological or infectious side effects

Abbreviations: CR, complete remission; IS, immunosuppressive; MCD, minimal change disease; UPCR, urine protein over creatinine ratio; f/u, follow up.

The efficacy of rituximab in the setting of CNI-dependent IMN was assessed in a small pilot prospective study. Thirteen patients with ≥4 CNI-responsive relapses while being weaned off and with glomerular filtration rate >60 mL/min were given 4 weekly doses of rituximab (375 mg/m^2). As a result, proteinuria decreased significantly from 2.5±0.76 g at baseline to 0.85±0.17 g at 6 months. CNIs and other immunosuppressant drugs could be stopped in all patients. Three patients relapsed but responded to a repeated course of rituximab. At 30 months, all patients were in remission.[24]

And finally, the results of the only randomized trial to date of rituximab in the management of IMN have been recently published.

GEMRITUX was a prospective, multicenter, RCT at 31 French hospitals. Seventy-seven patients with IMN and nephrotic syndrome despite 6 months of nonimmunosuppressive antiproteinuric treatment (NIAT) were randomized to either continue NIAT alone or the addition of rituximab 375 mg/m^2 on days 1 and 8. At 6 months there was no difference between the two groups with regards to the primary outcome of complete or partial remission, as 13 patients in the NIAT-rituximab group and eight patients in the NIAT group, achieved either complete or partial remission. However, rituximab achieved PLA2R-Ab depletion in 56% of patients after 3 months, and more patients in the rituximab reached a composite endpoint of decreased proteinuria of >50% and increased serum albumin of >30%, as compared to placebo (41% vs 13%, $P<0.01$). Another important finding during this trial was that patients with positive PLA2R-Ab at baseline, who achieved PLA2R-Ab depletion at month 3 after rituximab, had a higher chance of complete or partial remission, suggesting that PLA2R-Ab depletion may be a strong predictor of response to rituximab therapy in this setting. In contrast, B-cell depletion (which was achieved in all patients treated with rituximab) did not predict response to rituximab therapy. In the extended observational period of the trial (up to 24 months), significantly more patients in the NIAT-rituximab group achieved partial or complete remission as compared to NIAT group (64.9% and 34.2%, respectively, odds ratio, 3.5; 95% confidence interval, 1.7–9.2; $P<0.01$). There was no difference in side effects between the two groups.[25]

In summary, rituximab may be an effective alternative in the management of IMN. The results of GEMRITUX is a major step toward establishing the role of rituximab in the management of IMN, and importantly this trial found no increased side effects of rituximab as compared to placebo. However, more RCTs with longer follow-up (beyond 6 months as in GEMRITUX) are still needed to confirm the benefit and safety of rituximab both as first-line or second-line therapy as compared to the commonly used regimens of corticosteroids/cyclophosphamide, cyclosporine, and tacrolimus. Table 2 summarizes the characteristics of the discussed studies of rituximab in IMN.

Rituximab in FSGS

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the use of corticosteroids as first-line therapy for idiopathic FSGS with features of the nephrotic syndrome. Patients who remain resistant to steroids after at least 4 months, are treated with cyclosporine or high-dose dexamethasone with MMF. According to KDIGO, available evidence was insufficient to support the use of rituximab in FSGS.[4]

Only few reports have evaluated the use of rituximab in adult patients with FSGS, with variable results.

Fernandez-Fresnedo et al reported the use of rituximab in eight patients with FSGS resistant to steroids and other therapies. Only two patients had a sustained and significant reduction in proteinuria at 1 year and one patient had a significant but transient effect. All other five patients failed to respond to rituximab therapy.[26]

In another report from Japan, two patients with steroid-resistant FSGS did not respond to a single dose of rituximab. However, two patients with steroid-dependent FSGS achieved complete remission after a single dose of rituximab, which allowed discontinuation of steroids and CNIs. The two patients eventually relapsed, which coincided with CD19/20 positive B-cell count recovery, but they both responded again with sustained remission upon readministration of rituximab.[27]

In a recent study, rituximab was administered to 30 patients with steroid-dependent or frequently relapsing idiopathic nephrotic syndrome, and included five adult patients with FSGS. Over 1 year observation period, relapses decreased by approximately fivefold compared with the year preceding rituximab treatment. In addition, there was a subsequent reduced need for immunosuppressant medications in cases of recurrent disease.[28]

In summary, currently available evidence do not support a role for rituximab in the management of FSGS. RCTs are warranted to assess the possible benefit of rituximab in the management of steroid-dependent and frequently relapsing FSGS. Table 3 summarizes the characteristics of the discussed studies of rituximab in FSGS.

Table 2 Characteristics of discussed studies of rituximab in IMN

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Remuzzi et al[21]	Prospective, open label, single arm	Eight patients with IMN and urine protein of >3.5 g/day, despite full dose ACEI for 6 months	375 mg/m^2 every 4 weeks for 20 weeks	CR: proteinuria <1 g/day	Two patients achieved complete remission
				PR: proteinuria <3.5 g	Three patients achieved partial remission
				Mean proteinuria at 20 weeks	Mean proteinuria decreased from 8.6 to 3.8 g/day
				Side effects	Transient infusion-related reactions
Fervenza et al[22]	Prospective, open label, single arm	15 patients with IMN and severe nephrotic syndrome despite ACEIs or ARBs for 6 months (one lost to follow-up)	1 g on days 1 and 15	Change in mean proteinuria at 12 months	Mean proteinuria decreased from 13±5.7 to 6±7.3 g/day at 12 months
			Course repeated at 6 months for 3 g and B-cell recovery (ten patients were retreated at 6 months)	CR: proteinuria <3 g/day	2/14 at 12 months
				PR: proteinuria <3 g/day	6/14 at 12 months
				Side effects	Transient infusion-related reactions
Ruggenenti et al[23]	Prospective, open label, single arm	100 patients with IMN and proteinuria of >3.5 g/day, despite 6 months of ACEIs	4 weekly doses of rituximab 375 mg/m^2	Primary outcome: CR or PR defined as 24-hour urine protein excretion <0.3 or 3 g	65% achieved the primary outcome at 29 months. Median time to remission: 7.1 months
		Mean proteinuria at baseline was 9.1 (5.8–12.8)	Additional course was given if B-cell recovery	Side effects	No treatment-related adverse events apart from transient infusion reactions
Segarra et al[24]	Prospective, open label, single arm	13 patients with CNI-dependent IMN and GFR >60 mL/min	4 weekly doses of rituximab 375 mg/m^2	Percentage of patients who achieved treatment withdrawal	6 months after rituximab, CNIs and steroids could be withdrawn in all patients with no evidence of relapse
			Additional course was given if relapse (three patients)	Percentage of patients who maintained CR or PR 30 months after treatment withdrawal	At 30 months, all patients were maintained in remission
				Adverse events	No serious adverse events related to rituximab
Dahan et al[25]	Prospective, multicenter, randomized, controlled, parallel group trial	77 patients with IMN and nephrotic syndrome despite 6 months of NIAT	NIAT-rituximab group (intervention): NIAT + rituximab 375 mg/m^2 on days 1 and 8	Primary end point: percentage of patients with CR or PR at 6 months (CR: proteinuria <500 mg/day, PR: proteinuria <3.5 g/day)	No difference in primary end point at 6 months, however, the extended observational phase favored NIAT-rituximab group vs NIAT group: (64.9% vs 34.2% OR, 3.5; 95% CI, 1.7–9.2; $P<0.01$)
			NIAT group (control)	Decreased proteinuria of >50% + increase in serum albumin >30%	41% vs 13%, $P<0.01$ favoring NIAT-rituximab
				PLA2R-Ab levels	56% achieved depletion of PLA2R-Ab at 3 months in rituximab group
				Adverse events	No difference between the two groups

Abbreviations: ACEIs, angiotensin-converting-enzyme-inhibitors; ARBs, angiotensin-receptor-blockers; CI, confidence interval; CNIs, calcineurin inhibitors; CR, complete remission; GFR, glomerular filtration rate; IMN, idiopathic membranous nephropathy; NIAT, nonimmunosuppressive antiproteinuric treatment; OR, odds ratio; PLA2R-Ab, phospholipase A_2 receptor antibodies; PR, partial remission.

Table 3 Characteristics of discussed studies of rituximab in FSGS

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Fernandez-Fresnedo et al[26]	Retrospective case series	Eight patients with FSGS resistant to steroids and other treatments, all patients had nephrotic range proteinuria at baseline with a mean of 14±4.4 g/24 h	Variable: five patients received 4 weekly doses at 375 mg/m^2 One patient received 4 weekly doses at 375 mg/m^2 initially and again at month 12 One patient received 4 weekly doses at 375 mg/m^2 initially and 2 weekly infusions at month 6 One patient received 8 weekly doses at 375 mg/m^2	24-hour proteinuria Serum creatinine Adverse events	Two patients had significant decrease in proteinuria to 3.2 and 3.9 g/day One patient had transient decrease in proteinuria Five patients failed to respond to rituximab therapy with no significant decrease in proteinuria Serum creatinine increased from 1.4±0.5 to 2.2±1.8 mg/dL No adverse events during follow-up
Ochi et al[27]	Case series	Two patients with steroid-resistant FSGS, and two patients with steroid-dependent FSGS	Single dose at 375 mg/m^2	Complete remission (not defined in the manuscript)	CR achieved in the two patients with steroid-dependent FSGS The two patients with steroid-resistant FSGS did not respond to therapy
Ruggenenti et al[28]	Prospective, open-label, longitudinal, within-patient controlled study	30 patients (ten children, 20 adults) with steroid-dependent or frequently relapsing nephrotic syndrome (included eight patients with FSGS, five adults, three children)	Single dose at 375 mg/m^2 (28 patients) Or two doses of rituximab (two patients)	Number of relapse of nephrotic syndrome in the year after rituximab therapy vs the year before rituximab therapy Side effects	Fivefold decrease in number of relapse in all patients and in patients with FSGS No treatment-related adverse events

Abbreviations: CR, complete remission; FSGS, focal and segmental glomerulosclerosis.

Rituximab in IgAN

IgAN is the most common form of idiopathic glomerulonephritis worldwide. Recent studies have demonstrated that IgAN is an immune-mediated disease, with deposition of under-galactosylated, dimeric, or polymeric IgA in the glomerular mesangium. In addition, IgG or IgA autoantibodies directed against these abnormal IgA complexes might also contribute to the development and progression of IgAN, providing a plausible rationale for the use of immunosuppressive therapy in the treatment of IgAN.[29] Current guidelines, however, recommend antiproteinuric and antihypertensive therapy with ACEIs or ARBs as an initial therapeutic approach in IgAN patients with persistent proteinuria of >1 g/day, and a 6-month course of corticosteroids if the former approach was not successful after 3–6 months. Combination immunosuppressive therapy and the addition of cyclophosphamide and azathioprine was not advocated except in cases of rapidly progressive crescentic glomerulonephritis.[4]

The recently published Stop-IgA trial randomized 162 patients with IgAN, who had persistent proteinuria of at least 750 mg/day, despite a 6-month course of antiproteinuric supportive therapy, to continued supportive therapy alone, vs addition of immunosuppression. Corticosteroids monotherapy was used for patient with estimated glomerular filtration rate (eGFR) ≥60 mL/min, and a combination immunosuppressive therapy with corticosteroids, cyclophosphamide, followed by azathioprine maintenance for 3 years was used for patients with an eGFR between 30 and 59 mL/min. The results of this trial were disappointing, and although more patients in the immunosuppressive therapy group achieved a decrease in protein-to-creatinine ratio to <0.2 g/g, immunosuppression led to more side effects, and there was no difference between the two groups with regards to change in eGFR at 3 years. One of the limitations of this trial is the exclusion of patients with proteinuria of >3.5 g/day, who might have a better response to immunosuppressive therapy.[30]

Rituximab use in IgAN was reported in only a few patients. In a recent case series, rituximab was used to treat three kidney transplant recipients with biopsy-proven recurrence of IgAN. Recurrence of IgAN occurred at a median of 20 months posttransplantation, and the patients had a mean proteinuria of 4.8 g/day. Four monthly doses of rituximab at 375 mg/m^2 were given, and achieved a mean decrease of proteinuria of 3.1 g/day at month 6. Only one patient was treated initially with an ACEI, which was stopped after only 1 week due to increased serum creatinine level.[31]

In a prospective, single-arm trial, a single dose of rituximab at 375 mg/m^2 was given to treat 24 patients with primary glomerulonephritis, and included five patients with IgAN. After 6 months of the rituximab dose, there was no significant change in proteinuria in patients with IgAN (1.0±0.8 g/day at baseline vs 0.9±0.8 g/day at 6 months). Interpretation of the results of this trial was limited by the short follow-up of 6 months, and the possible need for several doses of rituximab to achieve response in a slowly progressive disease like IgAN.[32]

We await the results of a prospective, multicenter, randomized, controlled trial: rituximab in the treatment of progressive IgA nephropathy. In this trial, 54 patients with biopsy-proven IgAN, and proteinuria of >1 g/day, while on an ACEI, ARB, or a direct renin inhibitor, will be randomized to rituximab 1 g, on days 1, 15, 168, and 182, or to placebo. Change in proteinuria and kidney function will be assessed at 12 months.[33]

In summary, although the pathogenesis of IgAN may provide a plausible rationale for the use of rituximab, evidence is still lacking to date. The awaited results of the RCT presented in this section will help in clarifying the role of rituximab in the management of IgAN. Table 4 summarizes the characteristics of the discussed studies of rituximab in FSGS.

Rituximab in idiopathic MPGN

MPGN is a pattern of glomerular injury resulting from predominantly subendothelial and mesangial deposition of immune complexes and/or complement factors and their products.[29]

Current classification based on immunofluorescence findings divides etiology of MPGN into immune complex-mediated, characterized by capillary wall and mesangial deposition of C3 and immunoglobulin, and complement-mediated, characterized by capillary wall and mesangial deposition of C3, with negative immunoglobulins. Complement-mediated MPGN is usually secondary to abnormalities in alternate complement pathway.

Most cases of immune complex-mediated MPGN are secondary to infections (such as hepatitis C with or without cryoglobulinemia), autoimmune diseases such as systemic lupus erythematosus and monoclonal gammopathies. The diagnosis of idiopathic MPGN is established after all of these secondary causes are excluded. Therefore, truly idiopathic MPGN is decreasing in frequency, and currently considered a rare entity.[34]

The optimal therapy for patients with idiopathic MPGN is not clearly defined, and the latest KDIGO guidelines found

Table 4 Characteristics of discussed studies of rituximab in IgAN

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Chancharoenthana et al[31]	Case series	Three kidney transplant patients and recurrence of IgAN Proteinuria ranged between 3.4 and 5.5 g/day	4 monthly doses at 375 mg/m^2	Effect on proteinuria Adverse events	Mean decrease of proteinuria of 3.1 g/day at month 6 No treatment-related adverse events at 12 months
Sugiura et al[32]	Prospective, single-arm trial	24 patients with primary glomerular disease Included five patients with IgAN (proteinuria 1±0.8 g/day at baseline)	Single dose of 375 mg/m^2	Proteinuria at 6 months Adverse events	No change in patients with IgAN: 1±8 g/day at baseline vs 0.9±0.8 g/day at 6 months One patient had transient infusion-related reaction
Fernando Fervenza (ongoing trial)[33]	Prospective, multicenter, randomized controlled trial	54 patients with IgAN and proteinuria of >1 g/day	1 g, on days 1, 15, 168, and 182, vs placebo	Change in proteinuria and kidney function at 12 months	Pending

Abbreviation: IgAN, immunoglobulin A nephropathy.

very weak evidence to suggest the use of cyclophosphamide or MMF in combination with corticosteroids, in the treatment of patients with idiopathic MPGN with the nephrotic syndrome and progressive decline of kidney function.[4]

Few reports described the use of rituximab in idiopathic MPGN. In a retrospective case review study of 24 adult patients with primary glomerulonephritis who received rituximab, two patients with idiopathic MPGN were included. One patient presented with rapidly progressive glomerulonephritis and received two infusions of rituximab at 375 mg/m^2 each in addition to corticosteroids. Dialysis dependency was achieved after 5 months, and complete remission 19 months later (defined as UPCR <30 mg/mmol and serum albumin >35 g/L). The other patient presented with nephrotic syndrome, and achieved partial remission 29 months after a single dose of rituximab.[35]

In a prospective trial involving 24 patients with primary glomerulonephritis, a single dose of rituximab at 1 g was administered. The trial included one patient with idiopathic MPGN, who presented with nephrotic syndrome. The urine protein decreased from 9.8 g/day at baseline to 1.8 g/day at 6 months after the rituximab injection.[32] In another prospective trial, six patients with MPGN (four idiopathic and two with cryoglobulinemia), two doses of rituximab were administered at 1 g on days 1 and 15. The two patients with MPGN with cryoglobulinemia achieved complete remission after 12 months, while the four patients with idiopathic MPGN achieved partial remission (defined as reduction in the urine protein excretion of >50% to between 0.3 and 3.5 g/day without a doubling in the serum creatinine concentration).[36]

In summary, and despite the paucity of data, preliminary results for rituximab in the management of idiopathic MPGN are encouraging, which warrants a well-designed RCT comparing rituximab to other immunosuppressive agents in the management of idiopathic MPGN. Table 5 summarizes the characteristics of the discussed studies of rituximab in idiopathic MPGN.

Discussion

The available evidence supports the use of rituximab in the management of patients with MCD who are steroid-dependent or with frequently relapsing disease, and in the management of IMN.

In patients with steroid-dependent or frequently relapsing MCD, there is a need for well-designed RCTs with head-to-head comparison of the efficacy and safety of rituximab, vs other currently used agents, such as CNI, cyclophosphamide, and MMF. This trial should have an extended follow-up to properly assess sustained remission, episodes of relapse and safety of rituximab as compared to currently used second-line agents.

There is also a need for RCTs to establish the role and the risk–benefit ratio of rituximab as compared to steroids/cyclophosphamide or CNI, both as first-line or second-line agent in the management of IMN. Potential advantages of rituximab in this setting would include ease of administration, a more favorable safety profile as compared to cyclophosphamide therapy, and a less nephrotoxic potential as compared to CNI therapy. In fact, and apart from transient infusion reactions, most trials using rituximab in the treatment of primary glomerulopathies found no increased risk

Table 5 Characteristics of discussed studies of rituximab in idiopathic MPGN

Study	Study design	Population	Rituximab protocol	Selected outcomes	Results
Kong et al[35]	Retrospective case review	24 patients with primary glomerular disease	One patient received a single infusion of rituximab 375 mg/m^2	CR: UPCR <30 mg/mmol and serum albumin ≥35 g/L	One patient achieved CR after 19 months
		Included two patients with idiopathic MPGN	The other received two rituximab infusions at 375 mg/m^2	PR: UPCR between 30 and 300 mg/mmol and serum albumin ≥30 g/L	One patient achieved PR after 29 months
				Adverse events	No serious adverse events during follow-up
Sugiura et al[32]	Prospective, single-arm trial	24 patients with primary glomerular disease	Single dose of 375 mg/m^2	Proteinuria at 6 months	In one patient with MPGN, proteinuria decreased from 9.8 g/day at baseline to 1.8 g/day at 6 months
		Included one patient with idiopathic MPGN			
Dillon et al[36]	Prospective, single-arm trial	Six patients with MPGN (four idiopathic, two with cryoglobulinemia)	1 g on days 1 and 15	CR: proteinuria ≤0.3 g/day without doubling of serum creatinine	The two patients with MPGN and cryoglobulinemia achieved CR at 12 months
				PR: proteinuria between 0.3 and 3.5 g/day without doubling of serum creatinine	The four patients with idiopathic MPGN achieved PR at 12 months
				Adverse events	No adverse events during follow-up

Abbreviations: CR, complete remission; MPGN, membranoproliferative glomerulonephritis; PR, partial remission; UPCR, urine protein over creatinine ratio.

of serious hematologic or infectious adverse events. The results of GEMRITUX are encouraging, as it was the first RCT to test the efficacy and safety of rituximab therapy in the management of severe IMN, but this trial compared rituximab to placebo. The ongoing randomized controlled MENTOR trial will test another hypothesis, as it will assess the efficacy and safety of rituximab as first-line agent in the treatment of IMN, as compared to cyclosporine.[37] More RCTs like GEMRITUX are needed, although with a longer follow-up (beyond 1 year), to better assess remission rates and eventual episodes of relapse after rituximab therapy. Properly designed trials, and the results of the MENTOR trial will help in clarifying the optimal role of rituximab in the management of IMN.

In addition, the optimal infusion regimen and duration of rituximab therapy needs to be further clarified, as different infusion protocols were used in different trials, and B-cell repletion may not be the optimal predictor of disease relapse. In the setting of IMN, GEMRITUX, and previous data demonstrated that PLA2R-Ab depletion and not B-cell depletion predicted response to rituximab. The possibility of tailoring the rituximab infusion protocol according to PLA2R-Ab levels deserves further study.[20,25]

In contrast, results in FSGS are not as encouraging, likely suggesting a different underlying mechanism in FSGS whereby B lymphocytes are not the main role players. More trials are needed to establish the role of rituximab, if any, in the management of steroid-resistant or steroid-dependent FSGS.

On the other hand, the few reports that used rituximab in the setting of idiopathic MPGN are encouraging and warrant a formal RCT to assess the efficacy of rituximab compared to currently used regimens of cyclophosphamide or MMF with corticosteroids.

Evidence for the use of rituximab in the setting of IgAN is still lacking, and although recent trials have failed to demonstrate a significant benefit from immunosuppressive therapy for most patients with IgAN, the results of an ongoing RCT will help in clarifying the role of rituximab in patients with IgAN.[33]

Disclosure

The authors report no conflicts of interest in this work.

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