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Original Article

Rituximab as a Rescue Therapy in Patients with Glomerulonephritis

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ABSTRACT. To evaluate the use of rituximab in the treatment of severe glomerulonephritis (GN) in order to prevent progression of kidney disease toward the end stage, we designed a multicenter, retrospective study in Saudi Arabia about the efficacy and safety of the use of "off label" rituximab in a variety of severe refractory GN to conventional treatment and the progression of kidney disease for at least one year of follow-up. All the patients had kidney biopsies before treatment with rituximab, and proteinuria and glomerular filtration rate (GFR) were followed-up for the period of the study. The immediate side-effect at the time of administration of rituximab included itching in three patients, hypotension in one patient and anaphylaxis in one patient (dropped out from the study). After the administration of rituximab in 42 patients and during the first six months of therapy, 16 (38%) patients had complete remission (CR), 13 (31%) patients had partial remission (PR) and 13 (31%) patients had no remission. The mean follow-up period for the patients was 19.0 ± 6.97 months (median 18.0 months). The long-term follow-up during the study period disclosed a good hospitalization record for almost all of the patients. Membranous GN (MGN) was the largest group in the cohort (58% of the patients), and we observed CR and PR in 40% and 28% of them, respectively, which was comparable with the previous experience with rituximab in MGN patients with more CR than PR in our cohort. We conclude that our study suggests the safety and efficacy of the use of rituximab in patients with refractory GN and that larger and long-term prospective studies are required to define the role of rituximab in the different categories of these diseases.

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Introduction

Nephrotic syndrome is an important cause of chronic kidney disease (CKD) that may progress to end-stage renal disease (ESRD). The current treatment of the different types of glo-

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merulonephritis (GN) is still inadequate and with many-side effects, and the quest for novel and specific treatments for GN is needed, especially for resistant cases and for avoiding or delaying the progression to ESRD.

Injectable biologic drugs that neutralize B-lymphocytes, such as the chimeric anti-CD 20 (rituximab), have been proven efficacious in the treatment of non-Hodgkin's lymphoma, rheumatoid arthritis, autoimmune hemolytic anemia and renal transplantation.[1-5] These medications have been shown to induce remission of immune-mediated GN, such as membranous (MGN), IgA (IgAN) and focal segmental GN (FSGN), minimal change disease (MCD), lupus nephritis (LN) and vasculitis.[6-20]

Administration of rituximab has been associated with the release of proinflammatory cytokines such as tumor necrosis factor-alfa and interleukin 6, which may be responsible for the infusion-related adverse reactions.[1,2,21]

Rituximab causes a rapid and sustained depletion of circulating and tissue-based B-cells within the first three doses, with sustained depletion for up to six to nine months after treatment. B-cell recovery begins about six months following completion of the treatment course and median B-cell levels return to normal by 12 months. The median time to onset of remission is about 50 days and the median duration of remission is projected to be between 10 and 12 months.[1,20]

We aimed in this retrospective, multicenter study, which was conducted in different medical centers in Saudi Arabia, to evaluate the effectiveness of the off-label use of rituximab in the treatment of a variety of GN. We also aimed to evaluate its safety and efficacy as a kidney rescue therapy for the different types of GN causing refractory nephrotic syndrome and its ability to prevent progression of renal failure.

Methods and Patients

We studied the experience of ten medical centers in the Kingdom of Saudi Arabia in managing cases of GN (MCD, MGN, FSGS, MPGN, IgAN, SLE nephritis and other GN) in which rituximab was used off-label by the treating nephrologists as a rescue therapy to control the disease and prevent further deterioration of kidney function. Kidney biopsies were routinely performed and evaluated by histopathologists in all the reported cases. The effects of rituximab in all patients were monitored and followed-up by consultant nephrologists. The study was designed and coordinated and achieved the approval of its institutional review board (IRB) by the Saudi Center for Organ Transplantation in Riyadh, Saudi Arabia.

We included in the study adult patients with an age range from 18 to 70 years. Refractory nephrotic syndrome was defined as failure of one or more drug interventions, other than rituximab, to induce remission. These drugs include steroids, alkalyting agents, calcineurin inhibitors, mycophenolate, azathioprine, sirolimus, angiotensin converting enzyme inhibitors, angiotensin receptor blockers and plasmapheresis. The treated groups include patients with rapidly progressing kidney failure (GFR is decreasing >50% or doubling serum creatinine) at the start of the disease or during the aim-to-treat interventions; patients with relapsing nephrotic syndrome or experiencing treatment or intervention-dependent partial remission (PR) or complete remission (CR) with the aim of decreasing the rate of relapses or inducing nephrotic treatment-free remissions.

Each patient had a documented medical history and physical examination, including detailed history of renal disease, in addition to current therapies. Baseline laboratory investigations included complete blood count, liver function tests (aspartate transaminases (AST), Alanine transaminase (ALT) and alkaline phosphatase, albumin, total protein and bilirubin), electrolytes, calcium, phosphate, blood glucose, urea, creatinine, cholesterol and triglycerides. In addition, 24-h urine collection for proteinuria and GFR measurement on admission before and after rituximab infusion and morning urine protein/creatinine ratio on visits to the out-patient clinic for follow-up were also obtained. B-cell count and immunoglobulin profile assays at baseline and during the fol-

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low-up after rituximab infusion were obtained in some cases and some centers.

Details about the histopathology of the GN in each case in the study included glomeruli, tubules and interstitium. The degrees of glomerulosclerosis, tubular drop-out and interstitial fibrosis were reported as <25%, 25–50% and >50%, respectively. Glomerular filtration rate was estimated in each case using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

CR after rituximab therapy was defined as proteinuria <0.33 g/24 h and eGFR above 60 mL/min, PR as proteinuria <50% of the peak value or proteinuria from 0.33 to 1.5 g/24 h and GFR range from 30 to 60 mL/min and no response was defined as proteinuria above 1.5 g/24 h and/or GFR deteriorated below 30 mL/min or decreased 50% of the peak value.

For the administration of rituximab, all patients were hospitalized and circulating CD20 and CD19 B cells were counted by fluorescence-assisted cell-sorter analysis (if available) and relevant clinical and laboratory parameters including the tubular–interstitial score at pre-treatment biopsies were recorded. At the time of rituximab administration, all patients were pre-medicated for possible allergic reactions with antihistamine and steroids. The dose of rituximab was reconstituted in saline to a concentration of 1 mg/mL and was infused at an initial rate of 50 mL/h, then progressively increased according to tolerability with close observation for adverse events during the infusion. The dose of rituximab was calculated as 375 mg/m^2 and administered every week for two to four weeks. Some centers doubled the dose to give in half of the duration for administration. Repeating rituximab in case of recurrence of nephrotic syndrome (after PR or CR) was practiced in some centers.

Assessment of the efficacy of rituximab rescue therapy included follow-up of proteinuria and eGFR at each clinic visit. Hospitalizations and major events were recorded to evaluate the long-term follow-up of the patients. Repeated courses of rituximab and levels of B cells (if available) were reported during the follow-up.

Statistical Methods

Data were entered in a Microsoft Excel file. However, the description of data and analysis were performed using the statistical program (SPSS version 16).

All data were compiled descriptively in tables and frequencies. The analysis of the data addressed the validity of the data in connection with the key questions in the patients' files and end points.

Chi-square test was used throughout the analysis to test the significance of differences between groups and sub-groups for the non-continuous variables while the Student "t" test was used for the comparison of the means of the continuous variables. Statistical significance was set at P <0.05.

Results

There were 43 cases of use of rituximab rescue therapy reported from ten medical centers. The cohort included 24 (56%) males and 19 (44%) females with a mean age of 37.4 ± 9.46 years (median 34 years). There were 23 (53%) patients who had refractory nephrotic syndrome, ten (23.5%) patients with rapidly progressing kidney failure at the start of the disease or during the intention-to-treat interventions and ten (23.5%) patients with relapsing nephrotic syndrome or experiencing treatment or intervention-dependent PR or CRs.

Before receiving rituximab, 38 (90%) patients received immunosuppression (31 patients received prednisolone, 14 received MMF, nine received tacrolimus, eight received cyclosporine and five received cyclophosphamide), while five received only angiotensin converting enzyme inhibitors.

The mean baseline serum albumin before the use of rituximab was 34.1 ± 6.17 g/L and the median was 30 g/L. The baseline eGFR was 96.1 ± 46.1 mL/min and the median was 92 mL/min [41 patients (95%) had eGFR >30 mL/min and two patients <30 mL/min]. The mean baseline proteinuria was 6.24 ± 4.67 g/day and the median was 4.50 g/day [>1 g/day

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Table 1. Changes observed in the kidney biopsies in the study patients.

Percent of changes	<25%	25–50%	>50%
Glomerulorsclerosis	23	15	5
interstitial fibrosis	25	16	2
Tubular drop-out	25	16	2

in 37 (86%) patients, >2 g/day in 29 (67%) patients and >3 g/day in 25 (58%) patients].

The kidney biopsy was performed once in 38 (88%) patients and twice in five (12%) patients in case of vintage of the disease more than a year. All the kidney specimens were examined by light microscopy, while 37 of them required electron microscopy and immunofluorescence for final histopathological diagnosis. Table 1 shows the degree of the changes observed in the glomeruli, tubules and interstitium in the examined biopsies. The changes in most of the biopsies were modest in terms of glomerulosclerosis, interstitial fibrosis and tubular drop-out.

The mean of the cumulative dose of rituximab was 4000 ± 754 mg (over 2–8 weeks); 26 (61%) patients received a cumulative dose of 2000 mg, eight (19%) patients received 4000 mg, five (12%) patients received 1000 mg and the rest received variable doses of 500–1500 mg, while one patient did not receive the first dose and dropped out because of severe reaction to the drug.

The immediate side-effect at the time of administration of rituximab included itching in three patients, hypotension in one patient and anaphylaxis in one patient, who was dropped out from the study.

After the administration of rituximab in 42 pa-

Table 2. Details about the different histopathological categories of the patients treated with rituximab.

DX		NR	PR	CR	d/o	eGFR <30	eGFR >60	Hist. 1	Hist. 2	Hist. 3	Median F/up months	Hospitalization
MGN I	14	4	2	8	1	1	10	12	2		18	
MGN II	8	3	3	2		1	4	2	6		18	
MGN III	2	1	1			0	2		2		21	1 delivery
MGN IV	1		1			0	0		1		6	
MCD	2	1		1		0	2	2			6 and 12	
FSGS	3		2	1		0	3		2	1	21	
IgAN	1	1				0	0		1		12	1PD
MPGN	1			1		0	1	1			24	
LN DP	5	1	3	1		1	3	3	2		18	1 (pneumonia, cholecystitis, colitis)*
LN focal	1			1		0	1	1			12	
LN MGN	3	2		1		0	3	1	1	1	12	1 delivery
LN scleros	1			1		0	0			1	18	
Total	42	13 (31%)	13 (31%)	16 (38%)	1	3	29	22 (52%)	17 (40%)	3 (8%)	18	

FSGS: Focal segmental glomerulosclerosis, IgAN: anti-immunoglobulin A nephropathy, MCD: minimal change disease, MGN (I-IV): membranous glomerulonephritis grades 1–4, MPGN: memranoproliferative glomeruolonephritis, LN: lupus nephritis, DP: diffuse proliferative, scleros: sclerosis, NR: no remission (proteinuria above 1.5 g/24 h and/or GFR deteriorated below 30 mL/min or decreased 50% of the peak value), PR: partial remission (proteinuria <50% of the peak value or proteinuria from 0.33 to 1.5 g/24 h and GFR range from 30 to 60 mL/min), CR: complete remission (proteinuria <0.33 g/24 h and eGFR above 60 mL/min), eGFR: estimated glomerular filtration rate.

Hist 1: Minimal histological changes (glomerulosclerosis, tubular drop-out and interstitial fibrosis <25%), Hist 2: moderate histological changes (glomerulosclerosis, tubular drop-out and interstitial fibrosis 25–50%), Hist 3: severe histological changes (glomerulosclerosis, tubular drop-out and interstitial fibrosis >50%), F/up: follow-up, d/o: drop-out.

*All in one patient at different time intervals.

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Table 3. The comparison of response to rituximab according to the degree of the histopathological changes and functional status of the kidneys.

Comparisons		Remission with rituximab	No remission with rituximab	*P*-value
Moderate to severe histopathological changes	Yes	12	8	0.22
	No	17	5	
eGFR mL/min	≥60	20	7	0.53
	<60	9	6	
Mean proteinuria g/24 h	<3.0	12	4	0.12
	≥3.0	17	9	
Membranous glomerulopathy	Grade 1	14	10	0.67
	>Grade 1	7	4	

Moderate to severe histopathological changes: Glomerulosclerosis >25%, tubular drop-out >25% and interstitial fibrosis >25%. Response to rituximab: Partial remission (proteinuria <50% of the peak value or proteinuria from 0.33 to 1.5 g/24 h and GFR range from 30 to 60 mL/min) and also complete remission (proteinuria <0.33 g/24 h and eGFR above 60 mL/min).

tients and during the first six months of therapy, 16 (38%) patients had CR, 13 (31%) patients had PR and 13 (31%) patients had no remission. The mean follow-up period for the patients was 19.0 ± 6.97 months (median 18.0 months).

There was one patient who required repetition of the rituximab doses during the first year and two more at 1.5 years after the initial treatment to maintain the initial remission.

Table 2 shows the remission of proteinuria in response to therapy with rituximab in the different histopathological categories and the degree of the histopathological involvement, and baseline eGFR, median follow-up and hospitalizations of the study patients.

There were 25 (60%) patients who completed two years of follow-up after treatment with rituximab; of them, 18 (72%) patients had either a CR or PR. The comparison of the early with the late remission in those who completed two years of follow-up showed maintenance of remission (CR and PR) in all of them.

The comparison between the patients who responded to rituximab (CR and PR) and those with no response to the drug during the follow-up showed no significant differences between the patients with mild and those with moderate to severe histo-pathological changes. In addition, there were no significant differences between the patients with eGFR below 60 and those above 60 mL/min, or between the patients with 24-h proteinuria more than or equal 3 g and those below 3 g, or between the patients with low-grade MGN and those with high-grade MGN (Table 3). Finally, there were no differences in the mean 24 h baseline proteinuria between the responders and non-responders to rituximab therapy.

Discussion

The results of this study demonstrate the safety and efficacy of rituximab in causing remission in patients with different types of glomerulonephritis. The immediate side-effects due to infusion of rituximab were minimal and only one patient did not tolerate the drug. The follow-up during the study was uneventful with a good record of hospitalizations. The efficacy of rituximab was promising in the different categories of GN.

Idiopathic membranous nephropathy (MGN) is still the main cause of nephrotic syndrome in adults.[22,23] About 25% of cases are usually secondary to a predisposing disease such as SLE, infection or medical therapy.[24] Most of our cohort patients were in the category of MGN. The presentation and progression of the MGN dictate the levels of therapy.[25,26] Most patients are treated conservatively with renin–angiotensin system (RAS) blockade. If PR or CR is not achieved within six months of the conservative management, then immunosuppressive therapy is initiated with alkylating agents (cyclophosphamide or chlorambucil) or

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calcineurin inhibitors (cyclosporine or tacrolimus) in addition to corticosteroids.[27-30] Because of the limited efficacy, high rate of relapse and toxicities of immunosuppressive therapy, other modalities of therapy were pursued.

Recently, rituximab has been suggested as a treatment option for MGN,[6-9,29-31] based on the experimental evidence that B cell activation plays a role in the pathogenesis of MGN.[32] The response rate to rituximab included 15–20% for CR and 35–40% for PR, similar to the response rates of alkylating agents[28] and calcineurin inhibitors.[27] In our study, we found CR in 40% of the MGN patients and PR in 28% of them, and this was comparable with the previous experience[28] with rituximab in MGN patients with more CR than PR in our cohort.

The decision to treat with immunosuppressive medications is complicated by the well-known stable natural history of disease in most of the patients over a period of five to 10 years.[33,34] Some reviews found no significant difference in renal outcomes between immunomodulatory therapy and no treatment,[35] but some prospective studies found better survival with the use of immunosuppressive agents.[36] The efficacy of alkylating agents (and, to a lesser extent, calcineurin inhibitors) in treating MGN is attributed to their ability to interfere with B cell function,[35] and rituximab has similar potential with better profile in ease of administration, dosing, less side-effects and long-term effect.

The optimal dose of rituximab is 375 mg/m^2 rituximab, once weekly for four weeks,[3,29] or 1 g rituximab on Days 1 and 15.[30,31] Because there are still no general guidelines for the dosing for the GN diseases, the choices of the "off label" dosing protocols were variable in our study.

The effect of proteinuria on the long-term survival is still not clear, but treating it to reduce its toxic effect and to induce remission is a reasonable clinical goal, even with rituximab.[37] However, the limited toxicity profile of rituximab is primarily based on short-term data. The recent reports of progressive multifocal leukoencephalopathy is rare, but could be disastrous and cannot be neglected,[38,39] although this condition was reported in patients with autoimmune diseases not treated with rituximab and exposed to other immuno-modulatory drugs such as natalizumab, mycophenolate mofetil (MMF) and azathioprine.[40,41] All our patients remained alive and none of the patients had consequences to the use of rituximab during the study period, reflected by the low frequency for hospitalizations.

Rituximab was reported to be effective in inducing remission in adult and pediatric patients with multi-relapsing NS secondary to MCD, and also in those with steroid-dependent NS.[10-15] Furthermore, rituximab could induce remission in patients with recurrent FSGS in transplantation and native kidneys.[16-20,42] Moreover, there is a role for CD 19 associated with IgAN and consequently treatment with rituximab.[43] There were some cases in the category of MCD, FSGS and IgAN in our study with a promising response to rituximab, although the number of cases was very small and solid conclusions could not be made.

In recent years, rituximab has been used successfully in several renal autoimmune diseases as a part of a systemic disease such as rheumatoid arthritis (RA),[44] antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis[45] and systematic review in cryoglobulinemic GN.[46] The success of rituximab in these auto-immune diseases denotes a role for B cells in their pathogenesis. There were no cases of vasculitis in our cohort, although rituximab is labeled for use in this category of patients.

Resistant or relapsing LN occurs, respectively, 20% and 33% after first-line treatment.[47,48] In membranous LN, standard treatment is still inadequate and in patients with persistent severe nephrotic syndrome, effective therapeutic regimens with little toxicity are required.[49] MMF seems to be a promising treatment in both proliferative and membranous LN.[50] A recent study showed a good effect of rituximab in refractory LN,[51] while the LUNAR study did not show, in a randomized controlled design, an effect on the

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course of LN than mycophenolate–prednisone regimen in non-refractory cases.[52] The LN cases in our study showed a reasonable response to rituximab in all categories of LN.

Most of the side-effects (rigors, fever, headache, dyspnea, hypotension, bronchospasm, angioedema, abdominal pain and rash, neutropenia and thrombocytopenia) of rituximab related to infusion are possibly due to allergic reaction and/or release of proinflammatory cytokines. Infectious complications during the first six months after administration of rituximab include urinary infection, herpes zoster and influenza. The rate for hospitalizations with serious infection was very low in our study.

Rituximab can induce remission of proteinuria, but it does not "cure" the disease, stressing the need for long-term follow-up of these patients. A second course of rituximab has the potential to induce the production of human anti-chimeric antibodies (HACA). Formation of HACA after rituximab therapy is uncommon[53] and may be related to the effect of rituximab in abolishing primary and memory humoral responses.[54] The development of HACA may also be related to the dosage of rituximab, which may have an impact on the degree of B cell depletion.[47,55] Many centers in our study did not practice regularly in performing assays for the CD20 B cells or HACA. However, there were a few cases in which rituximab administration was repeated after the initial course.

The limitations in our study included the retrospective design and low number of patients in the different categories to make solid conclusions. However, the use of rituximab in GN patients was safe and its use in the membranous and LN categories was effective. In addition, rituximab has a more convenient protocol of administration in comparison with the other conventional therapies. The use of rituximab in prospective studies is warranted according to our study.

We conclude that our study suggests the safety and efficacy of the use of rituximab in patients with refractory GN and that larger and long-term prospective studies are required to define the role of rituximab in the different categories of these diseases.

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