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Clinical Response and Pattern of B cell Suppression with Single Low Dose Rituximab in Nephrology

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Abstract

Background There is no consensus regarding dose and frequency of rituximab in nephrology with extrapolation of doses used in treating lymphoproliferative disorders. There are no guidelines on targeting initial and subsequent doses on the basis of $CD19^+$ B cells.

Methods Initially, 100 mg rituximab was given to 42 adults with steroid-dependent nephrotic syndrome (SDNS) and frequently relapsing nephrotic syndrome (FRNS), idiopathic membranous nephropathy (MN), and high-immunologic-risk kidney transplantation. Absolute and percentage levels of CD19 B cells and clinical status were assessed at baseline, days 30, 90, and 180, and at 1 year. Subsequent doses of rituximab were on the basis of CD19 B cell reconstitution and clinical response.

Results CD19 B cell percentage decreased from 16.3 ± 7.6 to 0.3 ± 0.3 ($P \leq 0.001$), 1.9 ± 1.7 ($P \leq 0.001$), and 4.0 ± 4.5 ($P = 0.005$) by 30, 90, and 180 days, respectively. Suppression of CD19 B cell count below 1% at days 30, 90, and 180 was seen in 40 of 42 (95.2%), 18 of 42 (42.9%), and 7 of 42 (16.7%) patients, respectively. Of 30 with SDNS and FRNS followed up for 1 year, 29 (96.7%) went into remission at day 30. Remission was sustained in 23 (76.6%) at day 180 and 21 (70%) at 1 year. There was a significant decrease ($P < 0.001$) in the dose of steroids needed to maintain remission at 180 days after rituximab (0.27 ± 0.02 mg/kg to 0.02 ± 0.00 mg/kg). CD19 B cell percentage at 90 days correlated with relapse ($P = 0.001$; odds ratio 1.42; 95% confidence interval, 1.25 to 2.57). Eighteen (60%) required an additional dose. Of five with MN, four achieved remission by 6 months, which was sustained in three by 1 year. Of the seven kidney transplant recipients, two had antibody-mediated rejections, although CD19 B cells were suppressed even at 1 year.

Conclusions Low-dose rituximab induces sustained depletion of CD19 B cells for up to 90 days. Its role in preventing relapses in SDNS, FRNS, MN, and rejection needs further study.

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Introduction

Rituximab is an mAb targeting B cells and was initially used to treat B cell lymphoproliferative diseases (1,2). Subsequently, it has been used in nephrology practice for several diseases like vasculitis (3), SLE (4), frequently relapsing nephrotic syndrome (FRNS) (5), steroid-dependent nephrotic syndrome (SDNS) (6), membranous nephropathy (MN) (7), and the prevention and management of antibody-mediated kidney allograft rejection (8). The dose of 375 mg/m^2 weekly for 4 weeks used in the treatment of lymphoproliferative disorders (1) has been adopted by nephrologists (7). However, it is possible that a lesser dose and frequency than the current practice may be adequate in the treatment of non-neoplastic disorders. Although there are reports that pharmacokinetic studies show adequate B cell suppression with doses as low as 100 mg of rituximab (9), this dose did not gain popularity due to a paucity of clinical studies. Risk of short- and long-term side effects like allergic reactions, infections, progressive multifocal leukoencephalopathy, and developing anti-rituximab antibodies make it all the more justifiable to use the minimum dose and frequency in clinical practice if it proves efficacious (10).

Easy identification of B cell markers like CD19 and CD20 antigens using flow cytometry have provided the opportunity to target the dose and frequency of rituximab therapy (11,12). It is more than a decade since targeting CD19 B cell counts in MN resulted in limiting rituximab to a single dose with significant cost benefits without compromising its effect in decreasing proteinuria (13). All recent large trials in vasculitis and MN still recommend the dose and frequency used in managing B cell lymphoproliferative diseases (14–17). There are no clear guidelines about the efficacy of low-dose rituximab and targeting subsequent doses and frequencies on the basis of monitoring of CD19 B cell counts. We conducted a pilot study to evaluate the CD19 B cell suppression and clinical response to a single dose of 100 mg rituximab in nephrology practice. We also tested the feasibility and efficacy of dose adjustment guided by CD19 B cell counts during follow-up. Because we lacked a control group with

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Table 1. Baseline characteristics (at the time of first dose rituximab infusion) of the study participants

Characteristic	Frequently Relapsing Nephrotic Syndrome/ Steroid-Dependent Nephrotic Syndrome (*n*=30;3/27)	Membranous Nephropathy (*n*=5)	Transplant Recipients (*n*=7)
Age, mean (yr)	30.0 ± 11.2	55.2 ± 10.6	29.7 ± 6.1
Sex, *n* (%)			
Male	19 (63.3)	4 (80)	6 (85.7)
Female	11 (36.7)	1 (20)	1 (14.3)
Hemoglobin, mean (g/dl)	14.0 ± 1.9	13.2 ± 1.7	10.3 ± 1.5
Total leukocyte count, mean (number/μl)	8570 ± 2650	7650 ± 3210	6590 ± 4270
Absolute CD19 B cell count, mean (number/μl)	366 ± 225	318 ± 116	316 ± 208
CD19 B cell percentage, mean	16.2 ± 7.8	17.1 ± 1.6	14.5 ± 2.4
Platelet count, mean (number/μl)	280,000 ± 60,000	260,000 ± 70,000	220,000 ± 90,000
Serum creatinine, mean (mg/dl)	1.1 ± 0.5	1.3 ± 0.6	8.9 ± 6.4

conventional dose and frequency, we could not compare the efficacy of 100 mg rituximab with the former.

Materials and Methods

A prospective, single-center interventional study at a teaching hospital in South India was conducted from June 1, 2018 to October 31, 2019. The study was approved by the institutional ethics committee and was conducted in accordance with the Declaration of Helsinki. All patients provided informed written consent. Patients with SDNS, FRNS after renal biopsy, biopsy-proved primary MN with proteinuria > 4 g/d, and eGFR ≥30 ml/min per 1.73 m^2 and kidney transplant (KTx) recipients who had high immunologic risk were recruited. Immunologic risk was considered as high if the individual was donor-specific antibody-positive pretransplant, had a positive crossmatch due to IgM antibodies, or deceased donor renal transplantations with more than three of six HLA mismatch. We excluded those with age <12 years or >70 years, hepatitis B or C, HIV, or any other active infection, and those who had received prior rituximab injections.

Patients with SDNS and FRNS in relapse received 100 mg rituximab (Maball 100 mg, HETRO Oncology), a biosimilar of rituximab approved by the Central Drugs Standards Control Organization, India. Patients also received oral prednisolone 60 mg daily. After rituximab infusion, prednisolone was tapered to 10 mg on alternate days by day 60. Further tapering or stopping of steroids was done on the basis of clinical response. Individuals with SDNS and FRNS who required >10 mg alternate-day prednisolone to maintain remission also received 100 mg rituximab followed by tapering of prednisolone to reach 10 mg on alternate days by day 30, which was later tapered or stopped. Repeat doses of rituximab were given if the CD19 B cell count exceeded 1% after 30 days, when relapse occurred, and in those who did not achieve remission by 3 months.

Newly diagnosed MN patients with proteinuria >4 g/d and eGFR >30 ml/min per 1.73 m^2 received 100 mg rituximab as monotherapy in addition to maximum-tolerated doses of angiotensin receptor blockers, statins, and diuretics. Antibody titers to phospholipase A2 receptor (PLA2R) were checked in the sera of patients with MN before and periodically after rituximab.

Flow cytometry (FACSCanto II system) to determine CD19 B cell absolute counts and percentages were performed for all study participants at baseline, and at days 30, 90, and 180. Samples for baseline CD19 counts were sent just before administration of rituximab. KTx recipients received 100 mg rituximab on the day of or 1 day before transplantation surgery. They also underwent CD19 B cell monitoring at days 30, 90, 180, and 365. All KTx recipients received rabbit anti-thymocyte globulin for induction and mycophenolate mofetil, tacrolimus, and prednisolone as maintenance immunosuppression. KTx recipients with high immunologic risk who did not receive rituximab as induction in the year immediately previous to the start of this

Table 2. CD19 B cell suppression and clinical outcome (at the time of first dose of rituximab infusion) of the study participants

Time	Frequently Relapsing Nephrotic Syndrome/Steroid-Dependent Nephrotic Syndrome (n=30)	Membranous Nephropathy (n=5)	Transplant Recipients (n=7)
Day 30			
Absolute CD19 B cell count, mean (no/μl)	1.5±2.4	5.0±3.7	0
CD19 B cell percentage, mean	0.3±0.3	0.2±0.2	0
CD19 B cell suppression <1%, number (%)	28 (93.3)	5 (100)	7 (100)
Remission, number (%)	29 (96.7)	0	NA
Acute rejection episodes, number (%)	NA	NA	2 (14.2)
Day 90			
Absolute CD19 B cell count, mean (no/μl)	13.2±17.3	48.4±8.9	0
CD19 B cell percentage, mean	2.0±1.9	1.5±0.5	0
CD19 B cell suppression <1%, number (%)	10 (33.3)	1 (20)	7 (100)
Remission, number (%)	29 (96.7)	4 (80)[a]	NA
Acute rejection episodes, number (%)	NA	NA	2 (28.5)
Day 180			
Absolute CD19 B cell count, mean (no/μl)	155.0±162.8	79.0±12.3	0
CD19 B cell percentage, mean	6.2±4.8	4.1±0.3	0
CD19 B cell suppression <1%, number (%)	0	0	7 (100)
Remission, number (%)	23 (76.6)	4 (80)[b]	NA
Acute rejection episodes, number (%)	NA	NA	2 (28.5)
1 yr			
Remission, number (%)	21 (70)	3 (60)[c]	NA
Acute rejection episodes, number (%)	NA	NA	2 (28.5)

NA, not applicable.
[a]Partial remission in three, complete remission in one.
[b]Partial remission in two, complete remission in two.
[c]Partial remission in one, complete remission in two.

study were taken as historic controls. Although patients who received additional doses of rituximab were included to study clinical effects including proteinuria, they were excluded from further analysis of CD19 B cell suppression.

Rituximab at a dose of 100 mg was infused using a standard protocol. All patients were monitored post-treatment for relapse of nephrotic syndrome, infection episodes requiring hospitalization, reactivation of latent viral hepatitis and tuberculosis and acute rejection episodes after kidney transplantation.

Definitions

The following definitions are used henceforth: complete remission; reduction of proteinuria to <0.3 g/d or urine-protein creatinine ratio<300 mg/g; partial remission: reduction of proteinuria to 0.3–3.5 g/d (or urine protein-creatinine ratio 300–3500 mg/g) and a decrease >50% from baseline; relapse, proteinuria >3.5 g/d or urine protein-creatinine ratio >3500 mg/g urine creatinine after complete remission has been obtained; frequent relapse, Four or more relapses in any 12-month period; and steroid-dependent, two relapses during tapering or within 2 weeks of completing steroid therapy.

Statistical Methods

Data are presented as mean ± SD and results on categorical variables as number (%). The Shapiro–Wilk test was used to test the normality of the data. Means of two groups of continuous variables with normal distributions were compared by independent sample t test and those with non-normal distributions by Mann–Whitney U test. ANOVA was used to check if the means of more than two groups were significantly different from each other. The measurements made before and after an intervention were compared with paired t tests when normally distributed, and the Wilcoxon signed-rank test when non-normally distributed. Chi-squared and Fisher's exact tests were used to assess the significance of study parameters on categorical scales between two or more groups. Risk factors for relapse were assessed using regression analysis. Kaplan–Meier plotting was done to study the maintenance of remission. Significance was assessed at a 5% level of significance. Statistical software SPSS 22.0 and R environment version 3.2.2 were used to analyze data.

Results

Forty-two patients satisfying inclusion-exclusion criteria were enrolled. Of them, 27 (64%) had SDNS, 3 (7%) had

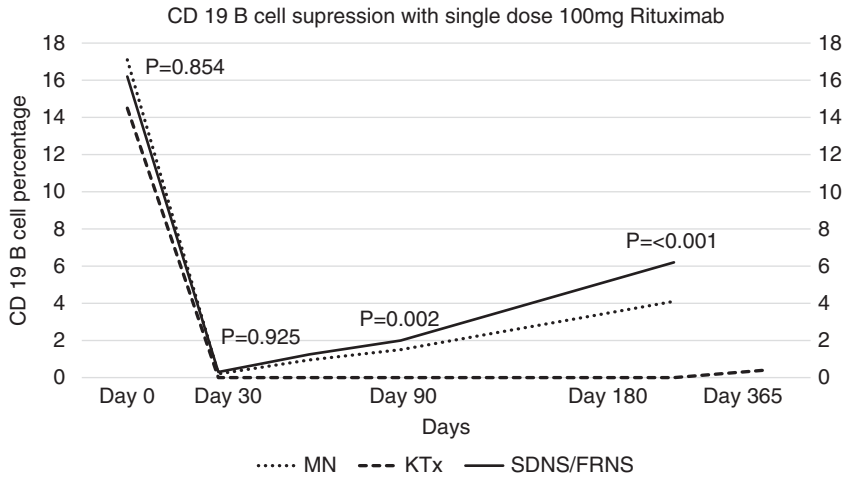

Figure 1. | **Pattern of CD19 B cell suppression with low-dose rituximab regime in SDNS/FRNS, MN, and KTx patients.** In one-way ANOVA, there is no statistically significant difference in the baseline CD19 B cell percentage (P=0.85) between the three groups. Suppression was comparable at day 30 (P=0.93). Suppression was significantly more in KTx recipients at days 90 (P=0.002) and 180 (P<0.001). FRNS, frequently relapsing nephrotic syndrome; KTx, kidney transplant; MN, membranous nephropathy; SDNS, steroid-dependent nephrotic syndrome.

FRNS, 5 (12%) had MN, and 7 (16.7%) were KTx recipients. Baseline characteristics of the study participants are detailed in Table 1. Of those with SDNS and FRNS, 24 had biopsy-proved minimal change disease and 6 had FSGS. The mean dose of oral prednisolone required to maintain remission in the SDRS/FRNS group was 15.2 ± 7.2 mg on alternate days.

The mean baseline absolute CD19 B cell count was 359 ± 303 and CD19 B cell percentage was 16.3% ± 7.2%. The mean absolute CD19 B cell counts and percentages at days 30, 90, and 180 were 2.0 ± 2.8 (0.3% ± 0.3%), 18.2 ± 20.5 (1.9% ± 1.7%), and 97.1 ± 137.7 (4.0% ± 4.5%), respectively (P<0.01). Table 2 shows the details for each group. The falls in CD19 B cells (percentages) when compared with baseline were significant at days 30 (P≤0.001), 90 (P≤0.001), and 180 (P=0.005) (Figure 1, Table 2). On day 30 after 100 mg rituximab injection, 40 of 42 (95.2%) patients had their CD19 B cell counts <1% of total lymphocytes. Suppression <1% at days 90 and 180 was seen in 18 of 42 (42.9%) and 7 of 42 (16.7%) patients, respectively. Mean CD19 B cell counts and percentages in renal transplant recipients at 1 year were 1.5 ± 1.7 and 0.3 ± 0.5, respectively. Baseline CD19 B cell percentages between the three groups were not significantly different (P=0.85). After 100 mg rituximab, CD19 B cell percentage suppression was comparable among the three groups at day 30 (P=0.93), but was significantly more suppressed in KTx recipients when compared with patients with MN and SDNS/FRNS at days 90 (P=0.002) and 180 (P<0.001).

Nephrotic Syndrome (SDNS/FRNS):

Of the 30 patients with SDNS/FRNS, 29 (96.7%) were in remission at 30 days. Remission was maintained in all of these 29 patients at 90 days, 23 (76.6%) at 180 days, and 21 (70.0%) at 1 year (Figure 2, Table 2). Details of CD19 B cell suppression in the SDNS/FRNS group are shown in Figure 1 and Table 2. By day 180, 16 SDNS patients were off steroids and 6 were on 5 mg prednisolone on alternate days. There was significant decrease (P<0.001) in the dose of steroids needed to maintain remission at 180 days after rituximab (0.27 ± 0.02 mg/kg to 0.02 ± 0.00 mg/kg). Eight patients received a second dose of rituximab after relapse and one due to repopulation of CD19 B cells at 1 month, although he was in remission. Eight others received a second dose between 6 and 9 months after B cell repopulation. One patient who did not achieve remission was given one more dose of 100 mg rituximab at 6 weeks. Although he went into clinical remission with disappearance of edema at 3 months, nephrotic range proteinuria persisted. Additional doses were required in 18 (60%) patients. None received more than two doses.

Figure 3 shows the timing of relapse in 29 patients who went into remission after 100 mg rituximab. Two patients relapsed in the fourth month, four in the fifth month, and one each in the seventh and 10th months. All eight patients who relapsed were treated with 100 mg rituximab and 60 mg oral prednisolone. All eight went into remission within 30 days. CD19 B cell percentages at 90 days were found to correlate with risk of relapse (P=0.001; odds ratio 1.42; 95% confidence interval, 1.25 to 2.57) (Table 3).

MN

Of five patients with idiopathic MN, two were positive for PLA2R antibodies. Details of their CD19 counts at baseline and after rituximab are shown in Figure 1 and Tables 1 and 2. After 100 mg rituximab, there was significant decrease in urine protein-creatinine ratio from baseline, at 90 days, at 180 days, and at 1 year (P<0.01) (Table 4). Two patients were in complete remission and two in partial remission at day 180. At 1 year, two patients continued to be in complete remission; one with partial remission had a further reduction in proteinuria and one patient with partial remission relapsed at the eighth month (Figure 2, Table 2). Although anti-PLA2R antibodies and proteinuria decreased initially in one patient by 30 days, he had worsening of proteinuria

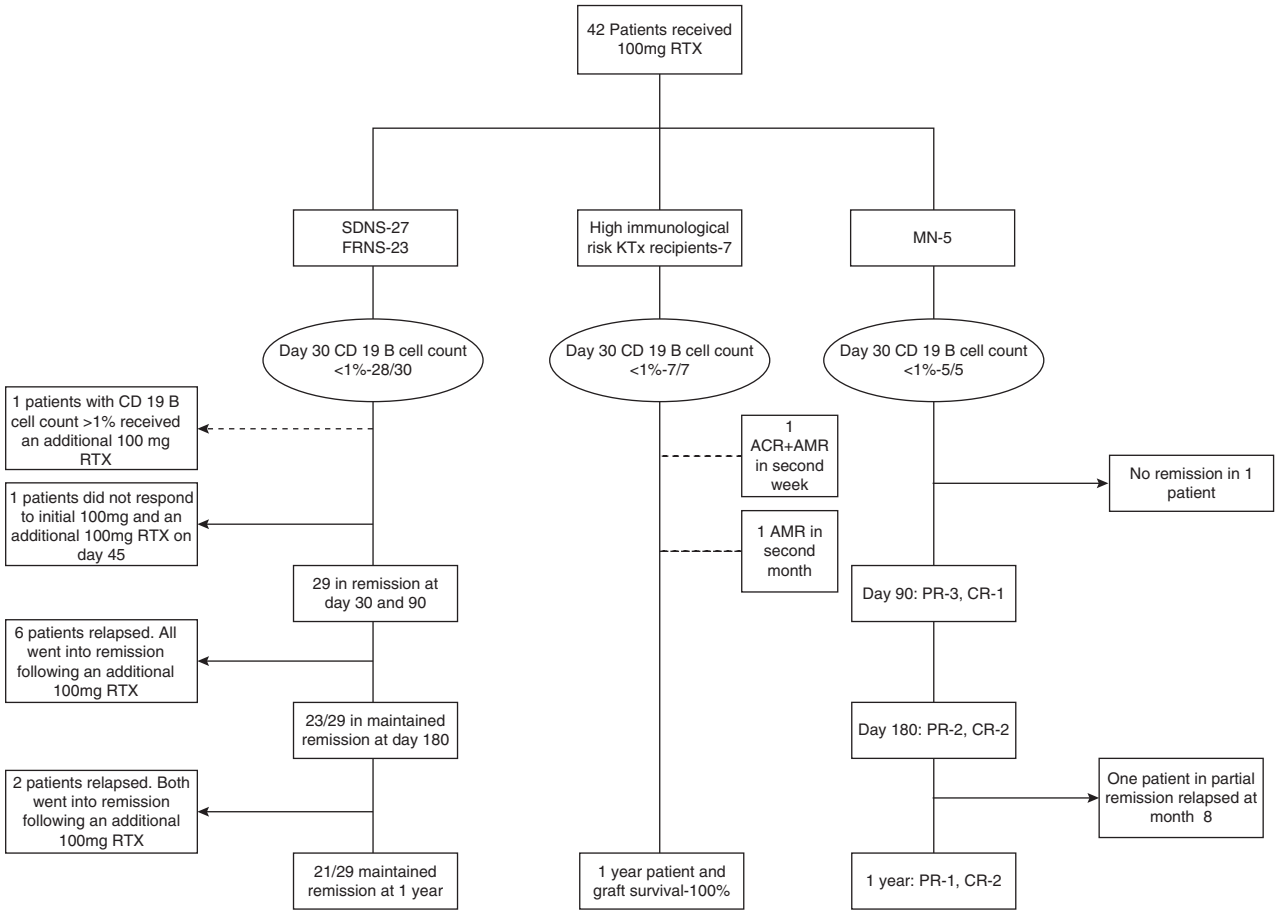

Figure 2. | **Flow chart of course of patients treated with 100 mg RTX.** RTX, rituximab; ACR, acute cellular rejection; AMR, antibody mediated rejection; PR, partial remission; CR, complete remission.

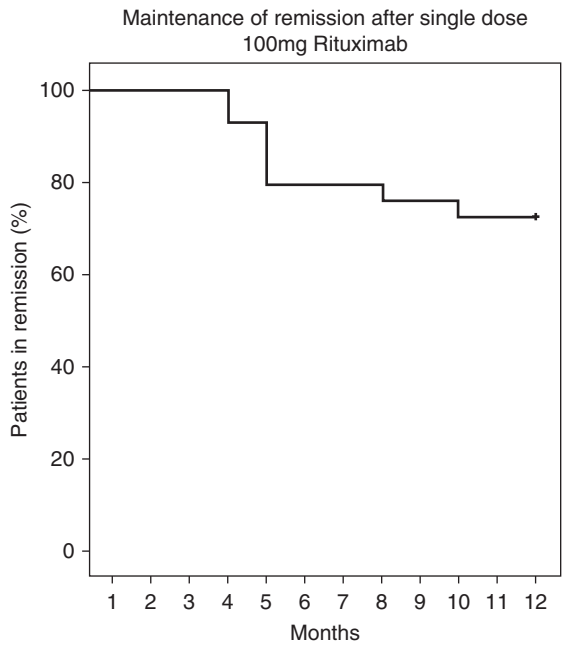

Figure 3. | **Kaplan–Meier curve showing responses of patients with SDNS and FRNS with 100 mg rituximab.**

with increased anti-PLA2R antibodies at day 90. Considering reports of better response with higher doses (16,17), he was subsequently given 500 mg twice weekly. Although this depleted the CD19 B cell count to zero with a partial fall in anti-PLA2R antibodies, proteinuria failed to decrease.

KTx Recipients

Of seven KTx recipients who received rituximab during the study period, three were deceased donor transplants and four were live donor transplants. Most had chronic GN although none had biopsy-proved MN. One had early combined cellular with humoral rejection in the first month and another had humoral-mediated rejection in second month. Both responded to steroids, plasmapheresis, and Ig. When compared with high-immunologic-risk patients who did not receive rituximab as induction (Table 5), rituximab did not have a significant benefit in preventing rejections ($P>0.99$), although CD19 B cells remain suppressed even at 1 year.

Side Effects

The clinical course and response to initial 100 mg rituximab is shown in Figure 2. Four (9.5%) patients had minor infusion reactions in the form of chills, which required temporary stoppage of the infusion. One patient became hepatitis B-positive with normal liver function tests at

Table 3. Risk factors for relapse for SDNS and FRNS after 100 mg rituximab

	P Value	Odds Ratio	95% Confidence Interval	
			Lower	Upper
Age	0.90	1.01	0.93	1.08
Sex (C)	0.51	0.54	0.09	3.37
Weight	0.50	1.02	0.96	1.09
Steroid dose	0.72	1.42	0.20	9.82
Number of relapses	0.37	1.09	0.91	1.30
Previous treatment with second-line agents	0.56	0.62	0.12	3.72
CD19 at baseline	0.24	0.92	0.80	1.06
CD19 at 30 d	0.69	1.57	0.17	14.92
CD19 at 90 d	0.001	1.42	1.25	2.57

90 days after rituximab injection. None had severe or life-threatening infections on follow-up.

Discussion

In this pilot study, which included SDNS, FRNS, MN, and high-risk transplant patients, we noted that a single low dose of 100 mg rituximab significantly suppressed CD19 B cell counts below 1% of total lymphocyte counts up 90 days with clinically significant responses in the majority of adult patients with SDNS and FRNS. Furthermore, this low dose was sufficient to reduce the dose of oral prednisolone to maintain remission at 90 days in 29 out of 30 patients without any relapse. Whereas response to rituximab has been shown previously in patients with SDNS and FRNS in both pediatric (18–20) and adult populations (21–23), the initial dose ranged from 375 mg/m^2 to 1000 mg (18,21). Multiple doses separated by 2–4 weeks were often given (21,18). The efficacy of rituximab in reducing the need for prednisolone has also been reported (24). The relapse that we observed in six patients after 90 days could be due to B cell reconstitution, considering that B cells may produce permeability factors that can cause proteinuria (25). Even though there are suggestions that rituximab may decrease proteinuria by targeting podocytes rather than B cells (26), monitoring the reconstitution of CD19 B cells could be a surrogate marker to suggest additional doses to prevent relapses (25).

Most patients with MN had decreases in proteinuria, with two going into complete remission. Although one patient had a significant decrease in their CD19 B cell count and anti-PLAR2 antibodies, he relapsed after 60 days with an increased PLA2R antibody level. The rise in PLAR2 antibodies could predict relapse or inefficacy of rituximab (27,28). There are reports that longer times may be required for MN patients to achieve remission, possibly due to delayed clearing of subepithelial immune deposits or PLA2R epitope spreading (29). Our results appear to be inferior when compared with 18 patients treated with higher doses, where 4 were in complete remission and 12 in partial remission by 2 years (17). Recently there has been a suggestion that a mega initial dose of 2 g of rituximab may provide a higher concentration for a prolonged time period, and may decrease the chance of epitope spreading and risk of relapse (30). In contrast, the efficacy of 100 mg rituximab has been reported to decrease CD19 levels in all patients with 50% going into remission (31). This could suggest that all patients with MN may not need a high initial loading dose of rituximab, although additional doses may be needed when B cell reconstitution occurs. Our observation of a failure to respond to subsequent higher doses when 100 mg was ineffective raises the possibility of resistance to rituximab in some, where higher doses may not be effective. Although few in number, our results also raise doubts regarding the need for a high initial dose when 100 mg suppresses B cells and can induce remission. Controlled studies comparing 100 mg rituximab with conventional higher doses with adequate sample sizes and prolonged follow-up may clarify these.

Rituximab in two doses of 1 g (32) as well as a single dose of 375 mg/m^2 (33) have been successfully tried as induction in highly sensitized patients awaiting renal transplantation. The efficacy of a single high dose of rituximab as induction has also been reported in live blood group A, B and O (ABO)-compatible renal transplantation (34,35) as well as in ABO-incompatible renal transplantation (36,37). Of seven high-risk renal allograft recipients in our study who received rituximab, two developed rejections that responded

Table 4. Urine protein-creatinine ratio in membranous nephropathy (*n*=5)

Urine PCR	Minimum	Maximum	Median	Mean	SD	*P* Value[a]
Baseline	8.60	12.00	9.80	9.80	1.56	—
90 d	1.30	6.80	4.30	4.15	2.62	0.002
180 d	0.15	8.02	1.2	4.91	3.11	0.001
1 yr	0.23	8.91	0.86	3.8	3.60	0.001

[a]Paired *t* test.

Table 5. Rejection rate

Rejection	Not Received Rituximab		Received Rituximab	
	Number	%	Number	%
No	6	66.7	5	71.4
Yes	3	33.3	2	28.6
Total	9	100.0	7	100.0

$P>0.99$.

to antirejection therapy. Successful use of low-dose rituximab has also been reported in ABO-incompatible renal transplantations (38). Although this, along with our observation of prolonged B cell suppression with 100 mg rituximab, could suggest that high doses may not be necessary in renal transplantation, this could not be confirmed in our study because it was underpowered, lacked a control group with a conventional dose of rituximab, and had limited follow-up.

Although we did not use low-dose rituximab in patients with lupus nephritis and vasculitis, there is a need to study its role in these situations on the basis of our observations. The role of rituximab was disappointing in reports of lupus nephritis (39) although reports on its use in resistant lupus have been advocated (4,40). Although a high dose was initially tried and recommended in vasculitis (41), giving an initial low dose and targeting further doses on the basis of CD19 B cell counts was also effective, suggesting a role for low-dose rituximab in vasculitis (42,43).

As B cells can remain suppressed for periods of $\leq$ 90 days with only a 100 mg initial dose of rituximab, as shown in our study and others (31,36,37,42), it suggests a role for lowering the high doses usually used in nephrological disorders (15,16,28,41). Higher initial doses may not influence the time available for B cell reconstitution (44,45). Although there were reports suggesting that a single dose of rituximab may be ineffective (46), our observations suggest that additional doses of rituximab spaced within 1 month of initial doses may not be necessary if there are no target B cells in circulation. Similar observations have been reported by others (31). Sustained B cell suppression can be achieved with much lower doses of rituximab if CD19 B cell counts are monitored and subsequent doses given only when B cells start to repopulate. CD19 B cell counts >1% or circulating B cells $>5/\mu$l could be taken as the threshold for further doses (13,31). Because sustained depletion of >80% of B cells has been reported for up to 6–9 months with rituximab (47), it is possible that even decreased frequency may suffice in some patients. None of our patients with SDNS and FRNS needed more than two doses during our follow-up period. Our observations suggest that monitoring for CD19 B cells after the initial 100 mg rituximab injection may be needed only for around 90 days as reconstitution of B cells starts then, with further doses given only if needed. This approach can be advantageous because it subjects the patients to a much lower cumulative dose of rituximab, possible toxicity, and risk of developing anti-rituximab antibodies (48). Although there are suggestions that monitoring the effect of rituximab on bone marrow cells may be preferable to peripheral B cell monitoring, because a single dose was noted to produce complete peripheral B cell depletion with persistence of B cells in secondary lymphoid organs (46), this may not be practical in clinical practice. Renal transplant recipients may be considered differently regarding the monitoring of CD19 B cells as they were seen to have sustained suppression even at 1 year after the initial dose, probably due to the bone marrow suppressive effect of maintenance immunosuppression, and may require less-frequent monitoring of B cell counts. Similar observations on B cell repopulation in renal transplantation have been made earlier (33). Reports also suggest that 100 mg rituximab for desensitization in ABO-incompatible transplantation has comparable clinical efficacy and B cell suppression when compared with 200 and 500 mg (37).

Costs of initial doses can be reduced by 1/20 if 100 mg is used instead of the usual dose. Cost-effectiveness will be more if hospital and nursing charges for additional infusions in the usual regime are also considered. Currently, 100 mg of rituximab (Maball) costs INR 6108.00 (USD 85.14) and 500 mg of rituximab costs INR 30,285.00 (USD 422.14). Although using a low initial dose of rituximab will require additional cost for subsequent monitoring of CD19 B cell counts and percentages [INR 1800 (USD 25.09) per test], it is still cost-effective. Similar cost savings with lesser doses have also been documented previously (13,31).

Rituximab infusion was well tolerated except for minor infusion reactions, although one patient became hepatitis B-positive. Similar reports of hepatitis virus reactivation had been documented (49). This would further suggest a need to avoidance of unnecessary high and repeated doses of rituximab. A need for subsequent doses could be considered if B cell repopulation occurs on the basis of clinical response.

There are several limitations to our single-center study with patients who were predominantly men and limited follow-up. Lack of a control group receiving the conventional dose and the frequency of rituximab limits comparison of a single dose of 100 mg in the time taken to induce and maintain remission in nephrotic syndrome, and its role in preventing rejections in high-risk renal transplantation. Our pilot study suggests the need for multicentre trials with a larger number of patients and follow-up to assess the role of a single low dose of rituximab, and that targeting subsequent doses on the basis of B cell repopulation has a role in nephrology practice considering lesser toxicity with cost benefits.

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Author contributions

J. George, S. Alex, and E. Thomas conceptualized the study; S. Alex, J. George, and E. Thomas were responsible for data curation; S. Alex, J. George, and E. Thomas were responsible formal analysis; S. Alex and E. Thomas were responsible for investigation; S. Alex, J. George, and E. Thomas were responsible for methodology; J. George, N. Gracious, N.S. Vineetha, and S. Kumar were responsible for supervision; all authors were responsible for writing

the original draft of the manuscript; and S. Alex, J. George, and E. Thomas were responsible for reviewing and editing the manuscript.

Disclosures

S. Alex, J. George, N. Gracious, S. Kumar, E. Thomas, and N. Vineetha have nothing to disclose.

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