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ORIGINAL ARTICLE

Short-term efficacy of rituximab versus tacrolimus in steroid-dependent nephrotic syndrome

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Abstract Although therapy with intravenous (IV) rituximab and tacrolimus reduces the relapse rate in steroid-dependent nephrotic syndrome (SDNS), studies on comparative efficacy are lacking. We retrospectively reviewed the records of patients with difficult-to-treat SDNS who had previously received levamisole, cyclophosphamide and/or mycophenolate mofetil, then treated with either rituximab or tacrolimus and followed for 12 months. Between January 2009 and April 2010, ten patients received two to three doses of IV rituximab (375 mg/m^2/week) and 13 received tacrolimus (0.1–0.2 mg/kg/day) for 12 months; none had previously received either agent. Patients received tapering doses of alternate-day prednisolone; other immunosuppressive agents were discontinued. The mean age of the patients at treatment initiation with rituximab and tacrolimus was 12.2±2.3 and 12.3±3.0 years, respectively. The respective pre-treatment relapse rates (3.1±1.1 and 3.5±1.6 relapses per year) and cumulative prednisolone dose (137.2±69.4 and 140.5±59.0 mg/kg/year) were similar. Therapy resulted in a decline in relapse rate in both groups ($P < 0.001$). The number of relapses in the rituximab and tacrolimus groups was similar at 6 months (0.3±0.5 vs. 0.3±0.6 episodes, respectively), 12 months (0.8±1.0 vs. 0.9±1.1 episodes) and last follow-up (1.2±1.0 vs. 1.5±1.3 episodes). There were no differences in relapse-free survival at 6, 12 and 18 months. Therapy resulted in a significant decline in the cumulative prednisolone dose (67.2% in the rituximab group and 43.6% in the tacrolimus group) and a reduced body mass index. These findings suggest that in our patients with difficult-to-treat SDNS, treatment with two to three doses of rituximab was as effective as 12 months of therapy with tacrolimus in terms of steroid sparing and reduction in the relapse rate.

Keywords Focal segmental glomerulosclerosis · Minimal change disease · Proteinuria

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Introduction

A significant proportion of patients with idiopathic nephrotic syndrome show frequent relapses or steroid dependence [1]. Although alternative medications, such as cyclophosphamide, levamisole and mycophenolate mofetil (MMF), reduce the frequency of relapses [2–4], the management of patients with steroid-dependent nephrotic syndrome (SDNS) refractory to these agents is challenging. Treatment with calcineurin inhibitors, such as cyclosporine or tacrolimus, is effective in reducing the frequency of relapses and achieves significant steroid sparing [3, 5, 6]. Since recent experience suggests that tacrolimus is as effective as cyclosporine in sustaining remission and has minimal cosmetic side effects, the former agent is preferred in patients with difficult-to-treat nephrotic syndrome [2, 7]. Other adverse effects, including nephrotoxicity, neurotoxicity, hyperlipidemia and hyperglycemia, limit the long-term use of both these agents [2, 3, 8].

During the last few years, rituximab has emerged as a promising treatment for sustaining remission in patients with difficult SDNS [9–13]. Encouraging results have been seen even among patients with calcineurin inhibitor toxicity or failure [9–12]. Reports on the use of rituximab prior to treatment with calcineurin inhibitors are limited [11, 13].

In view of our experience with rituximab, parents of patients with SDNS who have failed to respond to treatment with cyclophosphamide, mycophenolate mofetil and levamisole are counseled on available treatment choices. During the last 2 years, based on parental choice, such patients have initially received treatment with either oral tacrolimus or IV rituximab. Here, we report our review of the medical records of patients who were treated with either agent and followed for at least 1 year. The aim our study was to compare the efficacy of these two treatments. The outcome for three patients has been reported previously [11].

Methods

The Division of Pediatric Nephrology at the All India Institute of Medical Sciences, New Delhi is a referral center for children with kidney diseases in North India. Almost 400 new patients with nephrotic syndrome are referred annually. A proportion of these referrals are for the management of frequent relapses or steroid dependence.

Standard definitions were used for nephrotic syndrome, remission and relapses [2]. SDNS was defined as the occurrence of two consecutive relapses while the patient was receiving prednisolone on alternate days or within 15 days of its discontinuation. The initial therapy for these patients consisted of prolonged treatment with tapering doses of alternate-day prednisolone. Patients requiring a prednisolone dosage of >0.5 mg/kg on alternate days or showing steroid toxicity were treated with alternative medications, including levamisole (2 mg/kg on alternate days for 1–2 years), cyclophosphamide (2 mg/kg/day for 12 weeks) and/or MMF (600–1000 mg/m^2/day for 1–2 years) [2, 14]. Steroid toxicity was defined as a body mass index (BMI) of >2 standard deviation scores (SDS), height below −2 SDS or posterior subcapsular cataract [15, 16].

Patients who continued to show steroid dependence or steroid toxicity, despite therapy with at least two of the above alternative agents, were considered difficult-to-treat (difficult). Following counseling regarding efficacy, off-label use and potential side effects, parents were offered the choice of therapy either with tacrolimus or IV rituximab. The records were examined for patients with difficult SDNS who had received therapy with rituximab or tacrolimus between January 2009 and April 2010. Patients who had received prior therapy with any of these agents and those with impaired renal function [estimated glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 at beginning of therapy] or <12-month follow-up were excluded.

Therapy

Following informed consent and the induction of remission with prednisolone (2 mg/kg/day), IV rituximab was administered once weekly at a dose of 375 mg/m^2 for two or three doses, as described previously [11] with the aim of achieving CD19 depletion <1% of total lymphocyte count. Alternatively, patients were treated with oral tacrolimus at a dose of 0.1–0.2 mg/kg/day in two divided doses for 12 months, targeting trough levels between 4 and 7 ng/ml. Other agents (levamisole, MMF or cyclophosphamide) were withdrawn prior to rituximab or tacrolimus therapy. The dose of prednisolone was tapered (1.5 mg/kg on alternate days for 4 weeks, then reduced by 0.25 mg/kg every 2–4 weeks) and continued at a low dose (0.2–0.3 mg/kg on alternate days) while the patient was receiving tacrolimus. Prednisolone was tapered and discontinued over 3–4 months in patients treated with rituximab. Relapses were treated with the reinstitution of daily therapy with prednisolone (2 mg/kg/day) until remission, followed by alternate-day dosing (1.5 mg/kg) for 4 weeks and then either tapered (for patients receiving tacrolimus) or discontinued (rituximab group).

Patients having two or more relapses within 6 months or three relapses in 12 months were considered as treatment failure. Therapy was discontinued in these patients and in those showing medication-related toxicity (hyperglycemia, persistent increase in serum creatinine >50% above baseline, seizures or persistent headache).

Evaluation

Blood levels of creatinine, glucose, albumin, cholesterol and transaminases were monitored. Height and BMI SDS were estimated using the National Center for Health Statistics charts [15]. GFR was estimated at baseline and at 12 months using the modified Schwartz formula [17]. Hypertension was defined according to standard guidelines [18].

Statistics

Follow-up information at 6 months, 1 year and the last follow-up was compiled. The frequency of relapses, time to first relapse and cumulative prednisolone dosage (mg/kg/year) were compared between the groups. Values for continuous variables were expressed as mean ± standard deviation (95% confidence interval, CI). The outcome between groups was compared by the Fischer exact test and t test; P <0.05 was considered to be significant. The paired t test was used to compare the relapse rates and prednisolone dose within groups.

Results

Of 32 patients with difficult SDNS considered for therapy with either rituximab or tacrolimus, four did not consent due to cost of the medications and five were excluded due to prior treatment with a calcineurin inhibitor (n=4) or rituximab (n=1).

The baseline characteristics of 23 patients are shown in Table 1. Patients receiving rituximab (n=10) and tacrolimus (n=13) were similar in age at onset of nephrotic syndrome and at administration of therapy. Seven patients in the rituximab group and 12 patients in the tacrolimus group had failed to respond to prior therapy with all three medications, i.e. levamisole, cyclophosphamide and MMF. All patients had cushingoid features; a significant proportion were hypertensive (n=22, 96.5%) and/or overweight (BMI >2 SDS; n=11, 47.8%) or had short stature (height<−2 SDS; n = 14, 60.9%). Three patients had steroid-induced cataract. The renal histology was suggestive of minimal change disease in 13 patients, focal segmental glomerulosclerosis in three patients and mesangial proliferation in two patients; biopsy was not performed in five patients.

Of the patients administered rituximab, seven achieved CD19 depletion of <1% with two doses and three patients required an additional dose. Patients receiving tacrolimus showed adequate trough levels at 3–8 weeks from therapy initiation.

Relapse rates

Therapy with rituximab resulted in a significant decline in the relapse rate from 3.1±1.1 to 0.8±1.0 relapses/year (mean difference 2.3±1.4; 95% CI 1.3–3.3; P <0.001). A similar reduction in relapses, from 3.5±1.6 to 0.9±1.1 relapses/year, was noted during therapy with tacrolimus (mean difference 2.7±1.6 relapses/year; 95% CI 1.7–3.7; P < 0.001). Information on lymphocyte subsets, at time of relapse, was available for three patients; all showed recovery of CD19 levels to 11–19% of lymphocytes at 4–12 months of follow-up.

The number of relapses following therapy with rituximab and in patients receiving tacrolimus was similar at 6 months (0.3±0.5 vs. 0.3±0.6 relapses, respectively; P = 0.98) and at 12 months (0.8±1.0 vs. 0.9±1.1 relapses, respectively; P=0.92). The proportion of patients having infrequent or frequent relapses (treatment failure) was also similar (Table 2). Figure 1 shows that compared to the 6-months preceding therapy, patients in both groups showed a significant decline in the number of relapses at 6 and 12 months of follow-up.

The time to first relapse in patients given rituximab (8.5±5.1 months) was shorter than in those receiving tacrolimus (9.8±5.6 months); this difference was not significant (mean difference 1.3±2.8; 95% CI–4.7, 7.3; P=0.65). At the 1-year follow-up, similar proportions of patients in the rituximab (50%) and tacrolimus (46.2%) groups had sustained remission (P=0.93) (Table 2). Figure 2 shows that there were no differences in relapse-free survival at 6, 12 and 18 months among patients treated with rituximab or tacrolimus (log rank test, P=0.86).

Table 1 Baseline characteristics

Baseline characteristics	Rituximab group (n=10)	Tacrolimus group (n=13)
Age at onset, years	3.6±1.5	3.6±2.2
Age at steroid dependence, years	5.0±2.0	4.4±2.2
Age at therapy, years	12.2±2.3	12.3±3.0
Female, *n*	2	3
Height standard deviation score (SDS)	−2.2±1.1	−2.3±1.8
Body mass index SDS	2.0±1.1	1.7±0.8
Histology, *n*		
Minimal change disease	4	9
Focal segmental glomerulosclerosis	2	1
Mesangial proliferation	0	2
Relapses		
Preceding 1 year, episodes/year	3.1±1.1	3.5±1.6
Last 6 months, episodes/6 months	1.9±0.57	2.2±0.8
Cumulative steroid dose		
Preceding 1 year, mg/kg/year	140.5±59.0	125.7±58.2
Alternative therapy (%)		
Oral cyclophosphamide	10	13
Levamisole	7	13
Mycophenolate mofetil	8	12
Steroid toxicity, *n*		
Cataract	2	1
Hypertension	10	12
BMI >2 SDS	5	6
Height<−2 SDS	6	8
Blood investigations		
Albumin[a], g/dl	3.8±0.5	3.1±0.9
Cholesterol, mg/dl	221.3±40.2	295.8±151.1
Creatinine, mg/dl	0.60±0.14	0.63±0.16
Estimated GFR, ml/min/1.73 m^2	102.6±28.3	96.7±25.8

GFR, Glomerular filtration rate; BMI, body mass index

[a] All P values were non-significant except serum albumin (P=0.02)

Steroid sparing

Treatment with two to three doses of rituximab resulted in a significant decline in the cumulative dose of prednisolone from 140.5±59.0 to 46.1±42.1 mg/kg/year (mean difference 94.4±52.7; 95% CI 56.7–132.0; P <0.001). Similarly,

Table 2 Comparison of outcomes at the 1-year follow-up in patients with difficult steroid-dependent nephrotic syndrome

Outcomes	Rituximab group (n=10)	Tacrolimus group (n=13)	P value
Course of disease, n			0.93
Sustained remission	5	6	
1–2 relapses	4	5	
≥3 relapses	1	2	
Relapse episodes			
0–6 months	0.3±0.5	0.3±0.6	0.98
6–12 months	0.5±0.7	0.5±0.7	0.89
Cumulative steroid dose, mg/kg/year	46.1±42.1	70.9±26.3	0.11
Height SDS	−2.3±1.0	−2.4±1.5	0.85
BMI SDS	1.3±1.1	1.5±0.9	0.73
Change in BMI SDS	0.67±0.59	0.26±0.39	0.06
Blood Investigations			
Albumin, g/dl	3.8±0.6	3.4±1.3	0.33
Cholesterol, mg/dl	199±64.1	194.1±71.4	0.87
Creatinine, mg/dl	0.65±0.15	0.66±0.18	0.87
Estimated GFR, ml/min/1.73 m^2	97.2±31.96	93.7±23.80	0.80

SDS, Standard deviation score; BMI, Body mass index; GFR, Glomerular filtration rate

therapy with tacrolimus was associated with a decline in cumulative prednisolone dose from 125.7±58.2 mg/kg/year before therapy to 70.9±26.2 mg/kg/year (mean difference 54.8±48.8; 95% CI 23.9–85.8; P=0.003).

Table 2 shows that the cumulative prednisolone requirement during the 12-month follow-up was similar in the two groups (P=0.11). Therapy with prednisolone was discontinued in eight (80%) patients following rituximab treatment and in six (46.2%) patients during therapy with tacrolimus.

Height and BMI SDS

The height SDS did not change during the 1-year follow-up. A significant decrease in BMI SDS was noted in both groups. The BMI was reduced by 0.67±0.59 SDS (95% CI 0.24–1.09; P=0.006) in those treated with rituximab, and by 0.26±0.39 SDS (95% CI 0.03–0.50; P=0.03) in patients receiving tacrolimus.

Side effects

Adverse effects in patients treated with rituximab included infusion reactions in the form of chills, myalgia and transient skin rash (1 patient each). One patient receiving tacrolimus had reversible nephrotoxicity. No serious infections were noted during the follow-up period.

Outcome

Patients receiving rituximab and tacrolimus were followed for a mean duration of 15.9±4.7 and 19.7±4.8 months , respectively, without use of additional immunosuppressive drugs. At the last follow-up, the number of relapses in patients administered rituximab (1.2±1.0 relapses) and tacrolimus (1.5±1.3 relapses) were similar (P = 0.61). Four and three patients in the rituximab and tacrolimus groups, respectively, were in sustained remission, while four and five patients respectively showed frequent relapses (P=0.93).

Discussion

We report here a retrospective comparison of the efficacy of two promising immunosuppressive agents used for difficult SDNS, refractory to therapy with multiple drugs, including cyclophosphamide, levamisole and MMF. Our findings show that patients administered two to three doses of IV rituximab had a similar short-term outcome as those receiving 12 months of treatment with tacrolimus. The proportion of patients with sustained remission and frequency of relapses was similar at 12 months and the last follow-up. Therapy with both agents allowed steroid sparing and discontinuation of prednisolone in a sizeable proportion of patients that translated into reduction of the BMI. An advantage of therapy with rituximab was the requirement for two to three once-weekly doses with few side effects, most of which were infusion-related. However, therapy with this agent has been reported to be associated with severe adverse events, including acute lung injury [19] and progressive multifocal leukoencephalopathy [20].

Calcineurin inhibitors, including cyclosporine and tacrolimus, have been reported to reduce the frequency of relapses in 80–85% of patients with steroid dependence [3–5, 21, 22]. While recent studies suggest that the two agents have a similar efficacy in sustaining remission [6, 22], therapy with tacrolimus is preferred in view of fewer cosmetic side effects. The duration of treatment with calcineurin inhibitors is not defined, and most patients require long-term therapy. Prolonged therapy is associated with significant adverse effects, including glucose intolerance, seizures, headache, hypertension and dyslipidemia [23, 24]. Since histological evidence of nephrotoxicity is seen in 4–35% patients receiving prolonged therapy [3, 23, 24], there is a need to consider alternative agents that are effective and relatively safe.

Results from multiple case series highlight the effectiveness of therapy with IV rituximab in reducing the frequency of relapses and achieving steroid sparing in patients with difficult nephrotic syndrome [9–13, 25]. We previously

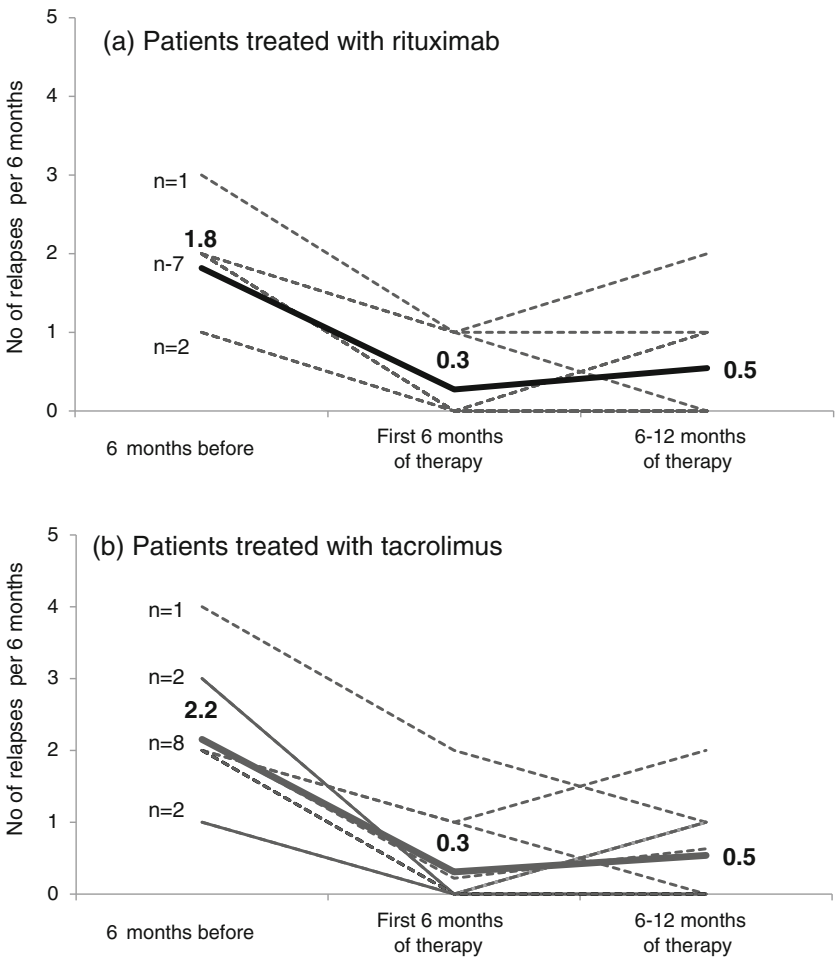

Fig. 1 Episodes of relapses 6 months before treatment initiation and at 0–6 and 6–12 months following therapy with rituximab or tacrolimus. *Dotted lines* Individual patients, *solid line* mean. **a** Therapy with rituximab resulted in a significant decline in relapses in the first 6 months and at 6–12 months of therapy ($P<0.001$ at each time point). **b** A similar reduction in relapses was noted following treatment with tacrolimus ($P<0.001$ at each time point)

reported that 83.3% of 24 patients with steroid dependence who received IV rituximab had sustained remission at 1 year [11]. In a multicentric case series, Prytula et al. reported that this agent induced sustained remission in 82% of 28 patients with steroid dependence who had previously received therapy with alkylating agents, calcineurin inhibitors and levamisole [12]. Guigonis et al. [9] showed that alternative immunosuppression could be withdrawn in 19 (86.4%) of 22 patients with difficult steroid or cyclosporine-dependent nephrotic syndrome. In most cases, therapy with rituximab has followed the long-term use of calcineurin inhibitors. However, two patients reported by Leclerc et al.

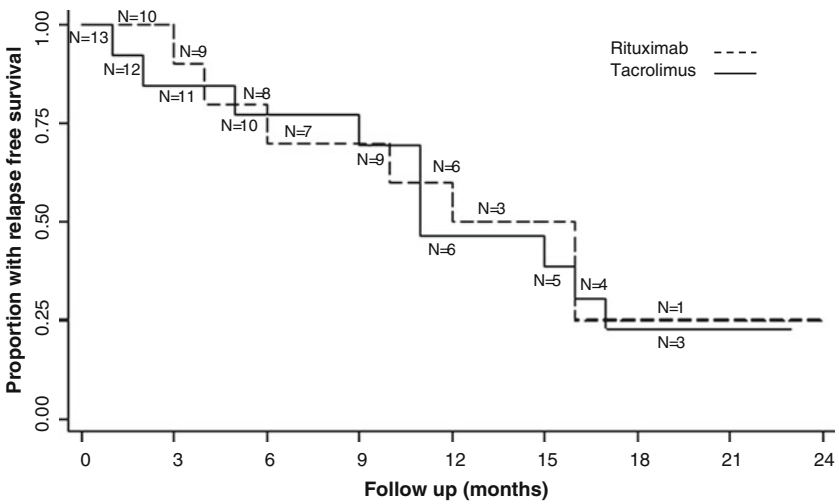

Fig. 2 Relapse-free survival in patients treated with rituximab (*dotted line*) and tacrolimus (*solid line*). Relapse-free survival was similar in the two groups at 6 months (70 vs. 76.9%), 12 months (50 vs. 46.2%) and 18 months (25 vs. 23.1%); logrank test $P=0.86$

and six patients in our previous cohort had received IV rituximab without prior treatment with calcineurin inhibitors [11, 13].

Recent reports suggest that the benefits of therapy with rituximab wane after 6–9 months, resulting in an increased risk of relapses [9, 10]. Relapse-free survival among our group of patients was 70 and 50% at 6 and 12 months, which is similar to recent reports from other centers [10, 26], but lower than that reported in our initial study [11]. While a recent study found satisfactory results in all 12 patients administered a single dose of rituximab, nine relapsed at 4 months and seven required additional doses of the medication [10]. In another case series, 18 (82.8%) of 22 patients required two to four courses of rituximab to sustain B cell depletion [13]. Ito et al. recently showed that administration of MMF following therapy with rituximab increased the proportion of patients in sustained remission at 1 year [26]. Further studies are therefore necessary to confirm whether the effects of rituximab are sustained with concomitant use of agents that specifically target B cells.

The limitations of this study are similar to those of any retrospective report, including possible selection bias and under-reporting of adverse effects. Patients in this study had difficult-to-treat disease refractory to multiple therapies, and it is not certain whether these findings can be generalized to all patients with SDNS. Our patients were highly selected, compliant and visited the hospital regularly, and the possibility of Hawthorne effect cannot be excluded. Although the magnitude of this effect cannot be estimated, the outcome assessment was relatively objective, and an observation bias seems unlikely. In the absence of routine monitoring of CD19 levels, information on B cell recovery and its relation to the occurrence of relapses was not available for patients treated with rituximab. Finally, the regimens for steroid tapering in the two groups were dissimilar and contributed to different cumulative steroid dose. Nevertheless, the significant reduction in frequency of relapses resulted in considerable steroid sparing in both groups.

In view of the limited number of prospective studies carried out to date, the place of rituximab in management of patients with difficult SDNS is not yet defined. Findings from this retrospective comparison highlight the need for a prospective, randomized controlled study comparing the efficacy of two to three doses of IV rituximab to 1-year therapy with tacrolimus in these patients. Demonstration of the non-inferiority of rituximab would allow the use of this agent in preference to calcineurin inhibitors. Alternatively, prospective studies may be designed to examine whether the combination of rituximab and MMF is superior to tacrolimus in ensuring sustained remission. Results from these studies are likely to further refine the therapy of patients with SDNS and provide an evidence base for effective and safe use of this agent.

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