



ORIGINAL ARTICLE

The efficacy of rituximab in adult frequently relapsing minimal change disease

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Abstract

Background: Corticosteroids are the basis of treatment for nephrotic syndrome due to minimal change disease (MCD), but 25% of patients have frequently relapsing nephrotic syndrome (FRNS) and 30% become steroid dependent. Prolonged use of conventional immunosuppressants causes significant toxicity. Rituximab (RTX) is now included in guidelines for childhood MCD. Evidence for use in adult MCD is limited. We describe a single-centre experience of RTX use in adult MCD.

Methods: Outcomes of all adult MCD patients treated with RTX for FRNS between 2008 and 2015 were retrospectively analysed.

Results: Thirteen patients received RTX; 11/13 had childhood-onset MCD. All had FRNS and 10 were steroid dependent. Eleven patients experienced one or more major treatment side effect from conventional therapy. At the time of RTX treatment, six patients were relapsing. All entered remission after RTX. The median length of follow-up after the first RTX treatment was 20 months (range 6–85). After RTX, the rate of relapse was reduced from 4 to 0.4/year (Wilcoxon signed rank $P \leq 0.05$). Seven patients relapsed after RTX after a median of 10 months (range 1–11). All seven relapsing patients were successfully re-treated with RTX and none developed RTX-resistant nephrosis. The median number of courses of RTX per patient was 1 (range 1–5). The number of additional immunosuppressants, steroid dependency and antihypertensive agents were also reduced. At the last follow-up, two patients remained on low-dose steroids. No RTX-related adverse events were observed.

Conclusion: RTX is safe and effective in adults with FRNS due to MCD. The median rate of relapse is significantly reduced following RTX treatment and additional immunosuppressant exposure is minimized.

Key words: frequently relapsing, minimal change disease, rituximab, steroid dependent

Introduction

Corticosteroids remain the foundation of treatment for nephrotic syndrome due to minimal change disease (MCD). While this achieves remission in the majority of patients, up to 90% of patients relapse; 25% relapse frequently and up to 30% become steroid dependent [1]. The prolonged use of steroids and additional immunosuppressive therapy can cause significant toxicity while persistent nephrotic syndrome can be complicated by infection, atherosclerosis and thrombosis [2].

MCD accounts for the majority of cases of nephrotic syndrome in children, with a peak incidence between 2 and 3 years of age; it also accounts for 10–15% of cases of nephrotic syndrome in adults [3]. Despite this, comparatively less research is available on the management and prognosis of nephrotic syndrome in adults, be it adult-onset MCD or childhood MCD persisting into adulthood [4, 5].

Rituximab (RTX) is a chimeric monoclonal antibody directed against the B-cell surface protein CD20 and induced B cell

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depletion. It has been used successfully in autoimmune diseases targeting the kidney, such as ANCA anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, lupus nephritis and membranous nephropathy. Recent trials have demonstrated sustained remission and a reduction in relapse rate as well as a significant reduction in dose or discontinuation of steroids and additional immunosuppressive agents in children with steroid-dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS) [4, 6, 7]. There have been case reports and small series to suggest that RTX is efficacious in adult patients with MCD [2, 8–11]. The pathophysiology of MCD remains poorly understood and the mechanistic involvement of B cells is not fully defined, but the reported efficacy of B cell depletion supports a pathogenic significant involvement [12, 13].

Materials and Methods

The study retrospectively analysed the outcome of 13 adult patients (>18 years old) with FRNS (defined as a mean relapse rate ≥ 2 /year) secondary to biopsy-proven MCD who were treated with RTX at a single institution over a 7-year period (July 2008–April 2015). The minimum follow-up period was 6 months. Patients had received at least one conventional immunosuppressant in addition to steroids, with or without steroid dependency. Steroid dependency was defined as two relapses during or within 2 weeks of stopping steroid therapy. A relapse was identified by the treating clinician as a substantial increase in proteinuria that warranted additional immunosuppression.

Data were obtained from hospital clinical databases. Medications given prior to RTX and drug-related toxicity were identified from patient records. A comparative analysis was then performed between the relapse rate, duration of remission and medications before and after RTX. Adverse events related to RTX were sought.

Twelve of 13 patients were initially treated with 2×1 g RTX infusions 2 weeks apart, reflecting the regimen used at this centre for patients with lupus nephritis and vasculitis. One patient who was relapsing at the time of initiation of RTX was treated with 4×500 mg infusions at weekly intervals due to concerns over enhanced drug losses from heavy proteinuria [8, 10]. Patients were considered for re-treatment with RTX in the context of disease relapse. CD19 counts were not routinely measured due to their inconsistency with predicting relapse as suggested by current literature [14].

Results

Baseline characteristics of patients prior to starting RTX treatment

Thirteen patients were treated with RTX. All but two patients had childhood-onset MCD, with the median age of onset of MCD being 4 years (Table 1). All patients had had prolonged steroid usage and 10 of 13 were steroid dependent since diagnosis. The median number of immunosuppressants taken in addition to steroids before RTX was four. Eight patients had undergone a second renal biopsy confirming histology in keeping with MCD and not focal segmental glomerulosclerosis (FSGS).

Eleven of 13 patients had one or more (median $n = 2$) side effects from conventional immunosuppressive therapy. Four patients were treated with bisphosphonates due to concern over osteoporosis risk, but only one patient had a reduced bone density confirmed by dual energy X-ray absorptiometry (DEXA) scan. Three patients developed diabetes mellitus (one insulin

Table 1. Patient demographics before RTX

Characteristic	n (minimum–maximum range)
Male	10
Female	3
British	10
Mixed race	1
Asian	2
Median age at onset of MCD (years)	4 (1–80)
Median age at initiation of RTX (years)	23 (19–83)
Previous immunosuppressive therapy	
Ciclosporin	11
Tacrolimus	8
Cyclophosphamide	9
Mycophenolate Mofetil MMF	8
Levamisole	5
Sirolimus	1
Azathioprine	2
Rapamycin	1
RTX ^a	1
Toxicity from previous immunosuppressant therapy	
Osteopenia	1
Diabetes mellitus	3
Hypertension (requiring treatment)	5
BMI >25	7
Infections (requiring hospital admission)	2
Calcineurin inhibitor-induced biopsy-proven renal damage	4
At initiation of RTX	
eGFR >90 mL/min/1.73 m ²	10 patients
Median serum creatinine (μ mol/L)	66 (45–151)
Median albumin (g/L)	42 (31–52)
Median urine albumin:creatinine ratio (mg/mmol)	58.5 (0–381.5)

^aOne patient had received one course of RTX 5 years previously at another institution under paediatric care and achieved remission but then reverted to prolonged steroid and calcineurin inhibitor use as the clinician's choice due to further relapses before transfer of care to the study institution.

dependent, two on oral hypoglycaemic therapy), two patients had infections requiring hospital admission, seven patients were overweight and five patients had developed hypertension requiring treatment. Four patients had biopsy evidence of calcineurin inhibitor (CNI)-induced renal damage.

At the time of initiation of the first treatment with RTX, seven patients were in remission and six were proteinuric (relapsing). The six proteinuric patients were receiving prednisolone 1 mg/kg at the time of RTX initiation.

After initiation of RTX treatment

Six patients had not relapsed at the end of follow-up; the median follow-up time for the non-relapsing patients was 17.5 months (range 6–38; Table 2). For the remaining patients, the median number of relapses since starting RTX was one, with the median time until first relapse being 10 months. The median duration of remission was 11 months, with a median follow-up time of 20 months. All patients were in remission at the last follow-up. Two patients were lost to follow-up.

Five patients had more than one course of RTX; the median number of courses of RTX was 1 (range 1–5). Patients were re-treated with Rituximab at the time of further relapse and also received a short course of high-dose prednisolone (1 mg/kg/day tapering) prior to administration of RTX at the treating clinician's

Table 2. Results after RTX

Variable	n (minimum–maximum range)
Median number of courses of RTX	1 (1–5)
Median number of relapses since starting RTX	1 (0–5)
Median time until first relapse (months)	10 (1–11)
Median duration of remission (months)	11 (1–38)
Median length of follow-up (months)	20 (6–85)
In remission at last follow-up (patients)	13 patients
Median time until steroid discontinuation for steroid-dependent patients (months)	4.5 (2–31)

Table 3. Comparison of results before and after

	Before RTX (minimum–maximum range)	After RTX (minimum–maximum range)
Median number of relapses/year	4 (2–6)	0.4 (0–0.9)
Median number of immunosuppressants (including steroids)	2 (1–4)	0 (0–1)
Number of steroid-dependent patients	10	2
Number of patients treated with anti-hypertensives	5	2
Median BMI	26.7	27.0

discretion. Two patients had an early relapse (within 4 months of a course of RTX) and were not re-treated with RTX on these occasions but went on to achieve sustained remission after a short tapering course of steroids. One other patient had a later relapse (after 10 months) and again achieved remission with a tapering course of steroids without RTX treatment; the patient went on to have four further courses of RTX following four further relapses.

One patient developed severe gut oedema due to nephrosis resulting in recurrent and protracted hospital admissions requiring high-dose steroids. He had relapsed three times following initiation of RTX treatment, receiving four courses of RTX at 12 monthly intervals to treat these relapses. A decision was therefore made to prophylactically treat with 1 g RTX every 6 months, of which he had received one dose at the end of the study and had not relapsed again.

The median number of relapses was reduced after RTX from 4 to 0.4 episodes/year (Wilcoxon signed rank $P \leq 0.05$) (Table 3). All patients were successfully weaned off all immunosuppressants, excluding steroids, after RTX. The median number of immunosuppressants (including steroids) taken before RTX was 2 and none after RTX. At the end of follow-up, 8 of 10 previously steroid-dependent patients discontinued steroids. The median time to steroid discontinuation for these patients was 4.5 months. One elderly patient on prednisolone 20 mg/day before RTX remained on 7.5 mg after RTX. A second patient who had been steroid dependent for 15 years was on prednisolone 15 mg/day before RTX and remained on 4 mg at the end of 4 months follow-up with a plan to discontinue steroids in the following months.

Of the six patients who were proteinuric at the time of initiation of RTX, five achieved complete remission after RTX. The other patient was steroid dependent prior to RTX and achieved partial remission (defined as >50% reduction in baseline proteinuria and a normal serum albumin) within a month of initiating RTX treatment. He did not relapse following this initial RTX or require additional steroids and remained off all other immunosuppressants.

There was no increase in the median body mass index (BMI) before and after RTX. The number of patients who required anti-hypertensive medications was reduced. The one patient with insulin-dependent diabetes no longer required insulin by the end of follow-up.

With regards to the side effect profile of RTX, by the end of follow-up none of the 13 patients experienced infusion or haematological reactions and none of the patients developed infections requiring hospitalization.

Discussion

This retrospective study describes a single-centre cohort of adult patients with FRNS due to MCD who required alternative treatment due to the burden of toxicity associated with the use of steroids and other immunosuppressants. Eleven of the 13 patients had childhood-onset MCD persisting into adulthood while only 2 of 13 patients had adult-onset MCD.

To our knowledge, the largest published case series to date reported that 14 of 41 (34%) adult MCD patients remained in remission after RTX (median follow-up of 39 months) [10]. Similarly, 6 of 13 (46%) patients described here remained in remission at the end of follow-up following a single course of RTX (median follow-up of 20 months). The median number of relapses per year decreased significantly. Seven patients relapsed after RTX but demonstrated sustained remission after re-treatment.

Eleven of the 13 patients had stopped all other immunosuppressant medications and steroids by the final follow-up. The two patients still requiring medication were both steroid dependent before RTX but had a substantially reduced steroid requirement at the final follow-up.

In this series, no patient experienced any serious adverse events related to RTX treatment, consistent with reported observations on the use of RTX in autoimmune renal disease.

These data support the use of RTX in adult patients with FRNS due to MCD.

Conflict of interest statement

I declare (and on behalf of the other co-authors) that the results presented in this article have not been published previously in whole or part, except in abstract form.

References

1. Fervenza F, Sethi S. Frequently relapsing, steroid-dependent minimal change disease: is rituximab the answer? *Nephrol Dial Transplant* 2013; 0: 1–7
2. Beco A, Castro-Ferreira I, Coentrao L et al. Rituximab for steroid dependent nephrotic syndrome. *Clin Nephrol* 2010; 74: 308–310
3. Waldman M, John Crew R, Valerie A et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol* 2007; 2: 445–453
4. KDIGO. clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012; 2: 1–274

5. Fakhouri F, Bocquet N, Taupin P et al. Steroid-sensitive nephrotic syndrome: from childhood to adulthood. *Am J Kidney Dis* 2003; 41: 550–557
6. Prytula A, Lijima K, Kamei K et al. Rituximab in refractory nephrotic syndrome. *Pediatr Nephrol* 2010; 25: 461–468
7. Ravani P, Magnasco A, Edefonti A et al. Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. *Clin J Am Soc Nephrol* 2011; 6: 1308–1315
8. Munityentwali H, Bouachi K, Audard V et al. Rituximab is an efficient and safe treatment in adults with steroid dependent minimal change disease. *Kidney Int* 2013; 83: 511–516
9. Francois H, Dugas E, Bensman A et al. Unexpected efficacy of Rituximab in multi-relapsing minimal change nephrotic syndrome in the adult: first case report and pathophysiological considerations. *Am J Kidney Dis* 2007; 49: 158–161
10. Guitard J, Hebral AL, Fakhouri F et al. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. *Nephrol Dial Transplant* 2014; 29: 2084–91
11. Bruchfield A, Benedek S, Hilderman M et al. Rituximab for minimal change disease in adults: long-term follow-up. *Nephrol Dial Transplant* 2014; 29: 851–856
12. Fornoni A, Sageshima J, Wei C AN et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 2011; 3: 85ra46
13. Haffner D, Fischer DC. Nephrotic syndrome and rituximab: facts and perspectives. *Pediatr Nephrol* 2009; 24: 1433–1438
14. Ferraro AJ, Smith SW, Neil D et al. Relapsed Wegener's granulomatosis after rituximab therapy—B cells are present in new pathological lesions despite persistent 'depletion' of peripheral blood. *Nephrol Dial Transplant* 2008; 23: 3030–3032