Rituximab in minimal change nephropathy and focal segmental glomerulosclerosis: report of four cases and review of the literature

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ABSTRACT

Minimal change nephropathy (MCNS) and focal segmental glomerulosclerosis (FSGS) are the main causes of the idiopathic nephrotic syndrome. MCNS usually responds to steroids and the long-term prognosis is generally good. However, some patients require prolonged treatment with immunosuppressive agents. FSGS generally follows a less favourable course: patients do not always respond to steroids and may progress to end-stage renal disease. Recurrence of FSGS after renal transplantation is frequently observed and may result in graft loss.

Recently, anecdotal case reports have described long-term resolution of nephrotic syndrome due to MCNS or FSGS after treatment with rituximab. We present four patients with nephrotic syndrome due to MCNS, FSGS or recurrence of FSGS after kidney transplantation, who were treated with rituximab with variable success. A review of the recent literature suggests that anti-CD20 antibodies may be a promising therapy, especially for patients with MCNS or idiopathic FSGS. Controlled studies are required to determine the efficacy of rituximab and to define which patients will benefit.

KEYWORDS

Focal segmental glomerulosclerosis, minimal change disease, nephrotic syndrome, recurrence, rituximab

INTRODUCTION

Minimal change nephropathy (MCNS) and focal segmental glomerulosclerosis (FSGS) are the main causes of the idiopathic nephrotic syndrome.

MCNS is typically seen in children with a nephrotic syndrome. Patients with MCNS usually respond to treatment with prednisone. However, in 40 to 50% of all patients the disease runs a frequently relapsing course, often requiring additional immunosuppressive treatment with agents such as cyclophosphamide or cyclosporine. The long-term prognosis is generally good, but up to 25% of frequent relapsers may need prolonged treatment with two or more immunosuppressive agents.[1] Cytokine release by T cells is supposed to play a key role in the pathogenesis of MCNS.[2] FSGS is considered less benign.[3] Patients do not always respond to steroid treatment and may progress to end-stage renal disease. Relapse of focal segmental glomerulosclerosis after renal transplantation is observed in 30 to 50% of all patients. In most cases, proteinuria recurs within two to four weeks after renal transplantation. If untreated, graft loss will occur.[4] FSGS is believed to be caused by a thus far unidentified circulatory permeability factor.[5,6]

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen which is present on B cells. Treatment with rituximab has been successful in patients with B cell lymphomas as well as in patients with autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or immune complex glomerulonephritis such as membranous nephropathy.[7-10] Recently several case reports have suggested that rituximab may be effective in the treatment of patients with MCNS and FSGS. In this report we describe four patients with a nephrotic syndrome due to MCNS or FSGS who were treated with rituximab because of failure of or intolerance to the standard immunosuppressive therapy. The short-term outcome of two patients has previously been described.[11,12] We also provide a review of the literature concerning the treatment of MCNS and FSGS with rituximab.

CASE REPORTS

Patient 1: MCNS

The medical history of this 20-year-old female patient and the short-term efficacy of rituximab has been described.[12] At the age of 2 years, she presented with nephrotic syndrome which responded to high-dose prednisone. However, the subsequent course was characterised by frequent relapses during childhood, despite treatment with various immunosuppressive therapeutic regimens consisting of prednisone, cyclophosphamide or cyclosporine. At the age of 18 years, the nephrotic syndrome was under control with the use of a low dose of prednisone (5 mg every other day) in combination with mycophenolate mofetil (MMF 1000 mg twice daily) and tacrolimus (target trough level 5 to 10 mg/l). Thereafter, the patient again developed relapses necessitating higher doses of prednisone. Ultimately remission could only be attained with very high doses of prednisone (60 mg/day). Heavy proteinuria (10 g/day) and low serum albumin (12 g/l) persisted while she was on prednisone (20 mg/day), MMF (1000 mg twice daily) and tacrolimus (15 mg twice daily, target trough level of 8-12 mg/l). This condition lasted more than a year and became intolerable. Therefore we decided to treat the patient with rituximab. She received two doses of 1000 mg intravenously with a two-week interval; MMF was stopped. Within two weeks there was a remarkable decrease in proteinuria (2 to 3 g/day) and an increase in serum albumin (21 g/l). Tacrolimus and prednisone were tapered and discontinued. Four months after the administration of rituximab, proteinuria was below 1 gram per day (*figure 1*). Return of CD20+ cells was observed after nine months. A relapse occurred 13 months after treatment with rituximab. Low-dose prednisone was not effective and the patient was again treated with rituximab (1000 mg, with a two-week interval). Administration of the first dose resulted in depletion of CD19+ and CD20+ B cells within two weeks. No adverse events occurred. However, during administration of the second dose of rituximab, she almost immediately developed hypotension, fever and dyspnoea. Antichimeric antibodies directed against rituximab proved positive. Despite B-cell depletion, heavy proteinuria (10 g/day) and a low serum albumin (6 g/l) persisted. The patient is currently being treated with pulse methylprednisolone (3 g intravenously), tacrolimus (7 mg twice daily, target trough level 5 to 10 mg/l) and oral prednisone (10 mg/day). Serum albumin is 16 g/l and proteinuria 4 g/day. The clinical course is complicated by a recurring erysipelas.

Patient 2: FSGS

This male patient with FSGS was treated with rituximab at the age of 20 years. At the age of 12 years, he presented with a nephrotic syndrome due to biopsy-proven FSGS. Treatment with prednisone (60 mg/m²) was initiated. After

Figure 1. *Course in terms of proteinuria and serum albumin and response to treatment with rituximab in patient 1, %CD19/20+ B cells is given*
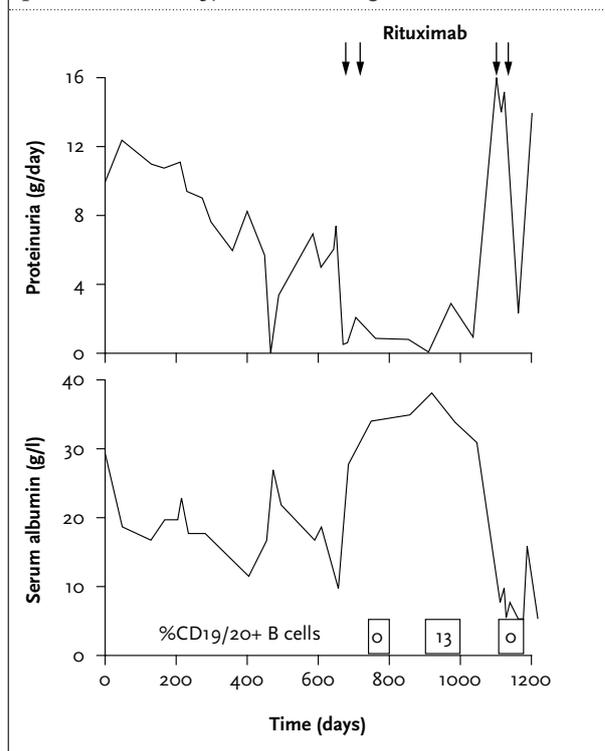
several weeks, cyclosporine was added because of persisting proteinuria and prednisone was replaced by mycophenolate mofetil. One year after presentation, proteinuria was 1 g/day and serum creatinine 90 μmol/l. At the age of 16 years, the patient again developed nephrotic range proteinuria. Cyclosporine was replaced by tacrolimus, leading to a temporary decrease in proteinuria but a rise in serum creatinine (140 μmol/l). A renal biopsy, performed three years after starting tacrolimus, showed 80% sclerosed glomeruli and moderate tubulointerstitial fibrosis. Tacrolimus was discontinued because of presumed toxicity and pulse methylprednisolone was administered (3 g intravenously) followed by oral prednisone (20 mg/day) with beneficial effects on proteinuria but not on serum creatinine. Renal function deteriorated and seven years after presentation serum creatinine was 170 μmol/l. At the age of 19 years, a relapse occurred during treatment with prednisone (10 mg/day) and mycophenolic acid (360 mg three times a day). Treatment with high doses of prednisone (60 mg/day) was initiated. This led to a complete remission, but during tapering of prednisone (to 25 mg/day) the patient experienced a relapse. We therefore decided to start treatment with anti-CD20 in this young male with high-dose steroid-responsive FSGS. Treatment consisted of two doses of rituximab (1000 mg intravenously) with a two-week interval. After the first dose of rituximab, mycophenolic acid was stopped and prednisone was continued in a dose of

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10 mg/day. Nephrotic range proteinuria persisted. Serum creatinine remained stable for six months but then renal function rapidly deteriorated necessitating renal replacement therapy.

Patient 3: FSGS

This 15-year-old male was treated with rituximab because of relapsing nephrotic syndrome due to FSGS. The patient presented with a nephrotic syndrome at the age of 7 years. A renal biopsy showed FSGS. Immunosuppressive treatment was started with cyclosporine and prednisone. Proteinuria gradually decreased and eventually a partial remission was attained. Three years after presentation a relapse occurred. Several courses of methylprednisolone (750 mg/day for three days) were given and mycophenolate mofetil was added to the immunosuppressive regimen. A partial remission was attained, but after six months a relapse occurred. High-dose prednisone therapy again led to a partial remission. Prednisone therapy was tapered and MMF was discontinued due to recurrent respiratory infections. Eventually cyclosporine was tapered and discontinued. At the age of 12, nephrotic range proteinuria recurred and the patient was treated with intravenous methylprednisolone, followed by prednisone and cyclophosphamide (2 to 3 mg/kg/day for 12 weeks). Partial remission was attained but tapering of prednisone to 25 mg every other day led to a rise in proteinuria. A renal biopsy performed six years after presentation showed 40% sclerosis of glomeruli and minor tubulointerstitial damage. Because of persisting proteinuria triple therapy was started at the age of 15. While on prednisone (tapered to 40 mg/day), MMF (1000 mg twice daily) and tacrolimus (5 mg twice daily, target trough level 7 to 10 mg/l), the patient experienced a relapse. Treatment with rituximab was started (1000 mg intravenously at a two-week interval). No adverse events occurred. Approximately one month after receiving the first dose of rituximab, a profound decrease in proteinuria (2.11 g/l to 0.31 g/l) combined with an increased serum albumin (26 g/l to 34 g/l) was observed (*figure 2*). Six months after receiving rituximab, CD19 and CD20 positive B cells were detected. Currently, ten months after the administration of rituximab, the patient has attained a complete remission while receiving minor doses of prednisone (3 mg every other day) and tacrolimus (2 mg twice daily).

Patient 4: recurrent FSGS after renal transplantation

The case report of this patient has been described by Deegens *et al.*[11] At the age of 10, she presented with a nephrotic syndrome due to biopsy-proven FSGS. End-stage renal disease developed despite treatment with prednisone, cyclophosphamide and cyclosporine. At the age of 13 she received her first renal graft. Recurrence of FSGS led to graft failure after one year. Seven years later, she received

Figure 2. *Course in terms of proteinuria and serum albumin and response to treatment with rituximab in patient 3, %CD19/20+ B cells is given*
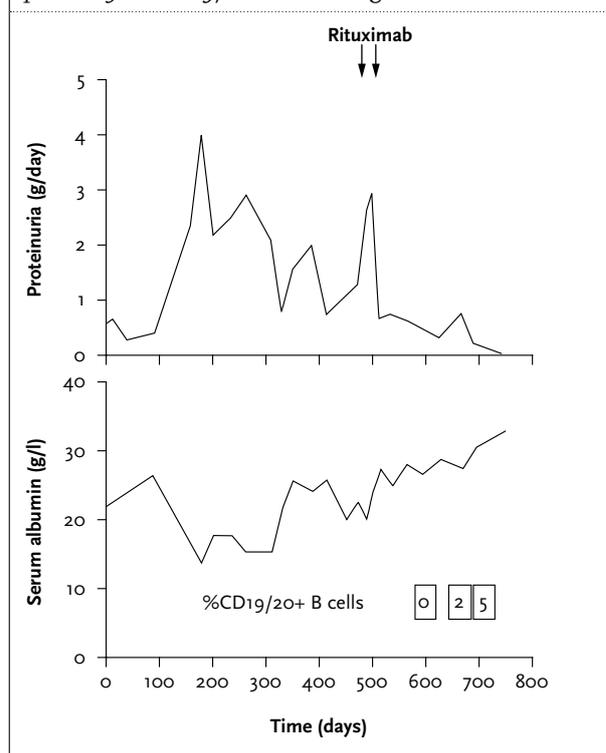
a second renal graft. Baseline immunosuppressive therapy consisted of prednisone (10 mg), tacrolimus (target trough level 15 to 20 mg/l) and mycophenolate mofetil (750 mg twice daily). There was almost immediate graft function. One week after transplantation, the patient developed nephrotic range proteinuria. Because of a presumed recurrence of FSGS, plasma exchange (PE) was started which resulted in complete remission. Proteinuria recurred, however, three months after cessation of PE while the patient was on prednisone (15 mg) and tacrolimus (target trough level 5 to 10 mg/l). A second course of PE (eight sessions) again resulted in complete remission. A third relapse occurred two years later. A biopsy of the renal graft demonstrated diffuse foot process effacement, without significant lesions on light microscopy and immunofluorescence, supporting a diagnosis of recurrent FSGS. A remission of proteinuria could only be maintained with continuous PE, even though the patient was treated with a more intensive immunosuppressive regimen consisting of prednisone (10 mg), tacrolimus (target trough level 5 to 10 mg/l), and MMF (500 mg twice daily), which was replaced by azathioprine (2 mg/kg/day) because of gastrointestinal side effects. Given PE dependence, it was decided to start treatment with rituximab. Apart from a temporary neutropenia, no significant side effects occurred during the course of four weekly infusions (375 mg/m²). After treatment

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B-cell markers CD19+ and CD20+ were undetectable. Increasing proteinuria required three PE sessions during the first four months after treatment with rituximab. Thereafter, proteinuria gradually decreased without further interventions. Seven months after treatment with rituximab a partial remission (proteinuria <2 g/day) was attained. Nine months later, she experienced a relapse of proteinuria. At that time CD19+ and CD20+ B cells were still undetectable. The patient was again treated with a single infusion of rituximab 1000 mg. Proteinuria gradually decreased and a partial remission was reached two months after treatment

DISCUSSION

We have described our experience with rituximab therapy in four patients with a nephrotic syndrome due to MCNS or FSGS. These cases suggest that rituximab may be effective in patients with nephrotic syndrome due to MCNS or FSGS. Admittedly, our data are anecdotal and controlled studies are required to prove the efficacy of rituximab. Nonetheless, we were impressed by the response in cases 1 and 3. These patients needed continuous treatment with various immunosuppressive agents for many years and ultimately remained severely nephrotic despite triple therapy with a calcineurin inhibitor, mycophenolate mofetil and prednisone. Following treatment with rituximab they developed a (nearly) complete remission while using no (case 1) or a limited dose (case 3) of immunosuppressive agents. In case 4, rituximab also appeared effective, although a response occurred slowly (after five months) and a contribution of plasmapheresis could not be excluded. The response to rituximab monotherapy after relapse, however, basically proved its efficacy. As illustrated by patient 2 and numerous case reports in the recent literature (*tables 1* to *3*), success varies. Furthermore, our cases illustrate a number of issues that may arise during treatment of nephrotic syndrome with rituximab, such as the relationship between proteinuria and circulating B cells and the potential development and role of antichimeric antibodies. We will discuss some of these issues briefly, after reviewing the literature on the treatment of nephrotic syndrome with rituximab.

MCNS
Table 1 provides an overview of the use of rituximab in patients with MCNS.[13-17] These reports have included both children and adults with a frequently relapsing nephrotic syndrome necessitating continuous immunosuppressive therapy. In all patients rituximab treatment resulted in a partial or complete remission of the nephrotic syndrome within two to ten weeks. In some patients concomitant immunosuppression could be stopped. In the study by Francois *et al*. remission was maintained while continuing

intermittent administration of rituximab.[14] Gilbert *et al*. successfully treated a relapse with a new course of rituximab.[13] In contrast, our patient did not respond to a second course of rituximab after relapsing. Of note, in our patient treatment was not given according to protocol due to the development of antibodies causing serum sickness.

FSGS
The first case suggesting benefit from rituximab in FSGS was described in 2004. In this 16-year-old boy, the diagnosis of FSGS was made when he was 2 years of age and its clinical course was characterised by multiple relapses, despite treatment with steroids, cyclosporine, cyclophosphamide and tacrolimus. Finally, he became severely dependent on steroids. Subsequently, the diagnosis of idiopathic thrombocytopenic purpura (ITP) was made in this patient. Neither steroids nor immunoglobulins induced permanent remission and it was decided to treat the ITP with rituximab. After treatment with rituximab no relapse of proteinuria or thrombocytopenia occurred. Since then, several case reports have described the effect of rituximab in FSGS.[16,18,19] So far, six patients (all children) with FSGS in their native kidney have been described, all of whom have been successfully treated (*table 2*). However, one must be aware of publication bias, since positive outcomes are more likely to be reported than negative ones. As illustrated by patient 3, treatment may fail. This could be due to the presence of irreversible damage before treatment with rituximab, considering the fact that renal biopsy showed 80% sclerosed glomeruli. Successful treatment with rituximab of a patient with FSGS and a diminished renal function has been described.[19]

Recurrence of FSGS after transplantation
Thus far, 15 patients (including patient 4) with recurrent FSGS after transplantation who received rituximab have been described.[20-28] An overview is given in *table 3*. These data suggest that response is variable and less favourable than in patients with MCNS or FSGS in their native kidneys. Moreover, interpretation of these data is difficult. In some patients who were treated successfully, rituximab was given to treat a coexisting posttransplant lymphoproliferative disorder (PTLD). It cannot be excluded that in these patients development of FSGS was related to the PTLD. In other patients rituximab was given in combination with plasmapheresis, making it impossible to draw conclusions on the efficacy of rituximab solely. On the other hand, response to rituximab may be slow as observed in patient 4, and consequently overlooked. Yabu *et al*. described a patient who did not respond within two months and received a short course of plasmapheresis. Thereafter proteinuria decreased from 6 to 1.9 g/day. In our

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Table 1. *Rituximab in patients with minimal change nephropathy*

Author	Sex	Age at diagnosis (years)	Age at start RTX (years)	RTX dose	Concomitant therapy	Response	Duration of follow-up	Comments
Gilbert	F	1.5	15	375 mg/m² once weekly, 4 doses	Deflazacort, tacrolimus	Remission, not specified	18 months	Relapse after 9 months. Response to steroids, relapse during tapering. After 16 months reinfusion (2 weekly doses), again remission. Ongoing treatment with low dose of prednisone
Francois	F	6	23	375 mg/m² once weekly, 4 doses	Prednisone, basiliximab (stopped before rituximab)	CR within 3 weeks	28 months	One year after first dose, reinfusion (2 weekly doses) because of detectable CD19/20 levels Persistent CR without immunosuppressive treatment
Smith	M	3	13	375 mg/m² once	Tacrolimus, MMF, prednisone	CR within 2 weeks	6 months	After 3 months return of CD19/20+ cells. Persistent CR, ongoing treatment with low doses of prednisone/ tacrolimus
Bagga	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR	14-58 weeks	Report of 5 patients with NS: 2 MCNS, 3 FSGS No differentiation between different patients possible. Ongoing treatment with prednisone and tacrolimus/CsA
	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR or PR	14-58 weeks	
Yang	F	40	40	375 mg/m² once weekly, 4 doses	Prednisone, MMF	CR within 10 weeks	12 months	CR, ongoing treatment with low doses of prednisone and MMF
Present study	F	2	20	1 g every other week, 2 doses	Prednisone, MMF, tacrolimus	PR within 4 weeks	16 months	PR for 12 months without immunosuppressive treatment. Relapse after 13 months, retreatment with RTX not effective

NS = nephrotic syndrome; MCNS = minimal change nephropathy; FSGS = focal segmental glomerulosclerosis; RTX = rituximab; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; CsA = cyclosporine; CR = complete remission; PR = partial remission; M = male; F = female; NA = not available.

Table 2. *Rituximab in patients with focal segmental glomerulosclerosis*

Author	Sex	Age at diagnosis (years)	Age at start RTX (years)	RTX dose	Concomitant therapy	Response	Follow-up	Comments
Benz	M	2	16	375 mg/m² once weekly, 4 doses	Prednisone, CsA	Remission, not specified	12 months	Treated for ITP, no relapses on CsA monotherapy
Bagga	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR	14-58 weeks	Report of 5 patients with NS: 2 MCNS, 3 FSGS No differentiation between different disease entities possible Ongoing treatment with prednisone and tacrolimus /CsA
	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR	14-58 weeks	
	NA	1-3.3	2.8-16.0	375 mg/m² once weekly, 4 doses	CNI, prednisone	CR or PR	14-58 weeks	
Nakayama	F	8	10	375 mg/m² once	Prednisone	CR within 8 months	14 months	PR after 1, CR after 8 months, no immunosuppressive therapy
	F	11	12	375 mg/m² once	Prednisone, CsA	PR within 1 month	14 months	Relapse after 8 months. After second course of RTX PR within 2 and CR within 5 months, ongoing treatment with prednisone
Present study	M	12	20	1 g every other week, 2 doses	Prednisone, MMF	None	7 months	80% of glomeruli showed sclerosis
	M	7	15	1 g every other week, 2 doses	Prednisone, tacrolimus, MMF	CR within 1 month	10 months	CR with low doses of prednisone and tacrolimus

NS = nephrotic syndrome; MCNS = minimal change nephropathy; FSGS = focal segmental glomerulosclerosis; ITP = idiopathic thrombocytopenic purpura; RTX = rituximab; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; CsA = cyclosporine; CR = complete remission; PR = partial remission; M = male; F = female; NA = not available.

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Table 3. *Rituximab in patients with recurrent FSGS after transplantation*

Author	Sex	Age at RTX treatment (years)	RTX dose	Concomitant therapy	Previous plasma exchange	Response	Follow-up (months)	Comments
Pescovitz	M	7	375 mg/m² once weekly, 6 doses	Tacrolimus, MMF (daclizumab)	Yes, response?	PR within 2 months	16	Treatment with rituximab because of PTLD
Nozu	M	12	375 mg/m² once weekly, 4 doses	CsA	No	CR within 7 months	36	Treatment with rituximab because of PTLD
Gossman	F	48	375 mg/m² once weekly, 2 doses	Prednisone, tacrolimus, MMF, ATG	Yes, no response	CR within 1.5 month	12	
El Firjani	F	48	375 mg/m² 6 doses in 8 weeks	Prednisone, tacrolimus, MMF, ATG	Yes, no response	None	NA	
Hristea	M	22	375 mg/m² once weekly, 2 doses	Prednisone, tacrolimus, MMF, basiliximab	Yes, partial response	CR after 3 months	24	PE and RTX were given concomitantly
Kamar	M	25	375 mg/m² once weekly, 2 doses	Prednisone, CsA, MMF, basiliximab	Yes, pre-emptive, partial response	CR within 1 week	10	PE and RTX were given concomitantly A relapse (within 1 month!) was also treated with RTX and PE
	M	46	375 mg/m² once weekly, 4 doses	Prednisone, CsA, MMF	Yes, no response	None	4	Proteinuria had already decreased before RTX was given
Marks	M	6	375 mg/m² once weekly, 4 doses	Prednisone, tacrolimus	Yes, but incomplete due to infections	None	5	No complete B-cell depletion
	M	10	750 mg/m² every other week, 2 doses	Prednisone, tacrolimus, MMF	Yes, partial response	None	14	No complete B-cell depletion No remission but stable at once weekly PE
Meyer	F	31	375 mg/m² once weekly, 3 doses	Prednisone	Yes, pre-emptive partial response	PR	14	One weekly dose not given because of UTI, decrease of proteinuria 5 months after RTX
Yabu	M	41	1 g every other week, 2 doses	Prednisone, tacrolimus, MMF	Yes, partial response	PR within 4 months	12	Received PE 2 months after RTX
	F	43	375 mg/m² once weekly, 4 doses	Prednisone, tacrolimus, MMF, ATG	Yes, partial response	None	10	Dialysis after 7 months, transplant nephrectomy after 10 months
	F	41	375 mg/m² once weekly, 4 doses	Prednisone, MMF, CsA, ATG, total lymphoid irradiation	Yes, no response	None	7	Stable serum creatinine (88 μmol/l) and serum albumin
	F	47	375 mg/m² once weekly, 4 doses	JAK3 inhibitor, MMF, prednisone	Yes, partial response	None	8	Stable serum creatinine (140 μmol/l) and serum albumin
Present study	F	24	375 mg/m² once weekly, 4 doses	Prednisone, tacrolimus, azathioprine	Yes, partial response	PR within 7 months	24	Relapse after 16 months, after second course of RTX PR within 2 months

PTLD = posttransplant lymphoproliferative disorder; **UTI** = urinary tract infection; **PE** = plasma exchange; **RTX** = rituximab; **CNI** = calcineurin inhibitor; **MMF** = mycophenolate mofetil; **CsA** = cyclosporine; **CR** = complete remission; **PR** = partial remission; **M** = male; **F** = female; **NA** = not available.

opinion a positive effect of rituximab cannot be excluded in this patient. Of note, in two out of eight nonresponsive patients, complete B-cell depletion was not achieved. Lastly, successful treatment of patients with recurrence of FSGS and a severely diminished renal function has been reported.[24, 25]

Overall, our case studies and a review of the literature suggest that anti-CD20 therapy may expand the therapeutic arsenal for patients with MCNS or FSGS. Controlled trials are needed to determine the true value of such treatment and more information is needed in order to determine which patients are likely to benefit.

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Immunoregulatory effects of B cells

Since FSGS and MCNS are not antibody-mediated diseases, the success of rituximab may seem surprising. However, B cells play an important role as immunoregulatory cells by both antigen presentation and cytokine release. Their elimination could have dampening effects on other immune cells such as T lymphocytes, dendritic cells, or macrophages. This hypothesis is supported by an observed reduction in activated T cells and a decrease in T-cell derived cytokines in patients with SLE and RA after treatment with rituximab.[29,30]

B-cell depletion and response

Administration of rituximab results in B-cell depletion. It is tempting to speculate that rituximab therapy may be monitored by measuring B cells. The data of our patients and those reported previously argue against an unambiguous relationship. Some patients do not respond despite B-cell depletion, others show a lack of correlation between the return of B cells and time of relapse. Similar observations have been made in patients with systemic diseases such as vasculitis or SLE.[9] From these studies it was suggested that measurement of circulating B cells does not accurately reflect the presence of B cells in other compartments, such as bone marrow, lymphoid tissue and organs. B cells residing in these nonperipheral compartments may be more resistant to depletion.[31] The presence of these residual cells could contribute to the disease and lead to a failure to respond or a relapse in the absence of circulating B cells. This phenomenon was observed in patient 4; no B cells were detected at the time of relapse of FSGS. Evaluation of the regeneration pattern of the subclasses of B cells after rituximab may also be important. In patients with RA, naive B cells returned within 12 months after treatment with rituximab, but CD27+ memory cells remained absent for a longer period of time.[32] This could explain why some patients remain in remission despite the return of B cells as is illustrated by patient 1 and other case reports.[15-19] Thus, monitoring of peripheral B cells cannot be used as an indication to repeat treatment with anti-CD20 antibodies, since the return of B cells does not appear to directly coincide with the return of disease activity. The decision to repeat treatment with rituximab should be based on clinical symptoms.

Kinetics of rituximab in proteinuria

In patients with non-Hodgkin's lymphoma (NHL), return of B cells was observed after six months and after 12 months B-cell counts had normalised in the majority of patients. Similar observations have been made in patients with RA. Fervenza *et al.* suggested that pharmacokinetic parameters may be different in patients with proteinuria since part of the administered antibody may be lost with protein-containing urine.[7] Rituximab levels were significantly lower in patients with idiopathic membranous nephropathy

when compared with patients with RA. Indeed, in patients with idiopathic membranous nephropathy return of B cells was observed after three months and normalisation of B cells was observed after six months. However, there was no correlation between rituximab levels and proteinuria. In another study in patients with nephrotic range proteinuria, B-cell counts remained subnormal for 12 months.[8] Thus, it is premature to draw firm conclusions regarding the effect of proteinuria on rituximab pharmacokinetics. Moreover, the relationship between rituximab levels and B-cell depletion needs further study.

Development of antibodies against rituximab

Due to the relapsing course of many nephropathies, it is likely that many patients will need repeated courses of rituximab. As indicated by the case history of patient 1, frequent administration of rituximab may lead to the development of antibodies. Since rituximab is a chimeric mouse/human antibody, it is less immunogenic than mouse monoclonal antibodies. Still human antichimeric antibodies (HACA) can develop. The reported incidence of HACA development varies widely. In B-NHL patients, HACA have been found in only one of 166 patients treated in the pivotal study, and in four of the 90 patients treated in another study.[33,34] In contrast, HACA were observed in six out of 14 tested patients with idiopathic membranous nephropathy and in 11 out of 17 patients with SLE.[7,35] The clinical significance of HACA is controversial. The presence of HACA could be expected to lead to a decreased response to rituximab due to accelerated clearance, and an increased incidence of serum sickness. Some studies showed a lower efficacy of rituximab in the presence of HACA.[35,36] In several other studies, however, no correlation between HACA and clinical response or infusion reactions was observed.[7,10,37] Of note, one patient with relapsed lymphoma was successfully treated with a second course of rituximab, despite the presence of HACA.[38] Our patient clearly shows that HACA can be problematic. Further studies should evaluate if the development of HACA can be suppressed by using concomitant immunosuppressive therapy at the time of administration of rituximab. In patients with RA, development of antibodies against infliximab is reduced by the use of methotrexate.[39] New humanised versions of anti-CD20 antibodies may ameliorate the problem of antibody formation.

CONCLUSION

Although anti-CD20 antibodies seem to offer a perspective for the treatment of patients with nephrotic syndrome due to MCNS or FSGS, positive results should be viewed with the necessary caution, since they may be overestimated due to publication bias. Controlled studies must be performed to prove the efficacy of rituximab, to evaluate its cost-effectiveness

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and to determine which patients will benefit. In the meantime it is important to establish guidelines for the rescue treatment of patients with steroid-dependent nephrotic syndrome. A nationwide registry could aid in finding early answers to some of the above-mentioned questions.

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