
Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance

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ABSTRACT

Background. Minimal-change nephrotic syndrome (MCNS) is a common cause of steroid sensitive nephrotic syndrome (NS) with frequent relapse. Although steroids and calcineurin inhibitors (CNIs) are the cornerstone treatments, the use of rituximab (RTX), a monoclonal antibody targeting B cells, is an efficient and safe alternative in childhood.

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Minimal-change nephrotic syndrome (MCNS) is the most frequent cause of acquired glomerular disease in children, and accounts for 20% of nephrotic syndromes (NS) in adulthood. MCNS results from a loss of the cytoskeleton organization at the level of the slit diaphragm, a highly differentiated molecular complex, which plays a crucial role in the maintenance of glomerular-filter permeability. Its pathogenesis remains elusive. To date, no MCNS-inducing soluble factor has been clearly recognized, or were identified in animal models but not validated in human [1, 2].

The efficacy of drugs that target cellular immunity, with steroids as the first choice, suggests that MCNS could be caused by a systemic T-cell function disorder. This hypothesis has been reinforced by the identification of common regulatory pathways between podocytes and T cells, involving the c-mip protein [3–5]. A number of alternative immunosuppressive drugs (ISs), including alkylating agents, calcineurin inhibitors (CNIs) and mycophenolate mofetil (MMF), have been tested in steroid-dependent or steroid-resistant patients with conflicting results and potential serious side effects. However, subsequent studies have shown that ISs may be effective as non-specific anti-proteinuric agents and that a defect of proximal signalling and cytoskeleton remodelling in podocyte may be the main molecular mechanism leading to MCNS [3, 6]. Therefore, new drugs with safer profiles need to be tested for the treatment of this disease.

Rituximab (RTX) (Rituxan®/MabThera®, Roche Pharmaceuticals, Basel, Switzerland) is a chimeric monoclonal antibody that targets CD20+ lymphocytes, resulting in B-cell depletion. In 2006, Gilbert et al. [7] described the first successful use of RTX to treat steroid-dependent MCNS. Although the patient experienced sustained remission after infusion of RTX, a relapse occurred shortly after B-cells became detectable. Thereafter, RTX has been used in an increasing number of children with MCNS [8–12]. In adults, its efficacy was first demonstrated in a young woman with MCNS and high-level steroid dependency, in whom complete steroid withdrawal with sustained remission (follow-up >5 years) was observed [13]. Additional case reports suggest that RTX may be effective in adults with MCNS [14, 15]. More recently, Munyentwile et al. [16] reported on a cohort of 17 adult patients with MCNS who received RTX. In this study, 12 of the 17 patients (70%) no longer needed IS drugs by the end of the follow-up (29.5 ± 18.2 months). A relapse occurred in 6 of the 12 patients that achieved a complete remission (mean time 11.4 months).

Whether RTX is efficient and safe in adult patients with MCNS needs further clarification. The aim of our study was to gather data on the prescription, efficacy and tolerance of RTX in patients with MCNS in order to evaluate potential indications, and to pave the way for randomized prospective studies. In this observational, multicentric, retrospective study, we extensively describe the clinical course of 41 adult patients with MCNS and receiving RTX.

**INTRODUCTION**

**MATERIALS AND METHODS**

We retrospectively reviewed the clinical charts of all consecutive patients with a diagnosis of MCNS and who received RTX between March 2006 and September 2012. Patients were followed in 11 renal units in France (University Hospitals of Toulouse, Nantes, Amiens, Rennes, Nice and Bordeaux; Bichat and Tenon University Hospital, Paris; Annecy and Bourg-en-Bresse Hospital) and in Belgium (UCL, Brussels). This study was conducted according to the Declaration of Helsinki, as recommended by French Law. Use of RTX in patients with MCNS and long-term immunosuppression (steroids, CNIs) or a contraindication to steroids was approved by our Immunology Review Board.

We enrolled adult patients who presented with biopsy-proven MCNS and who had received RTX after the age of 15 years. Given that NS with a normal first biopsy can be misdiagnosed as MCNS but evolve to focal segmental glomerulosclerosis (FSGS), patients were excluded if a biopsy performed within the first 5 years of evolution showed signs of FSGS. Patients who received RTX to treat a disease other than MCNS (for instance lymphoma) were also excluded, as were patients with concomitant thymoma, and patients with steroid-resistant NS.

**Clinical assessment**

Clinical histories were recorded through standardized screening of the patients’ hospital records. Haematuria and leukocyturia were assessed by urinary dipstick analysis, and a direct examination if available. Proteinuria was assessed by measurement of a 24-h urine sample or by assessing the urine protein/creatinine (uPr/Cr) ratio. Estimation of glomerular filtration rate (eGFR) was calculated using the simplified
Modification of Diet in Renal Disease formula. Renal failure was defined by an eGFR of <60 mL/min/1.73 m², and the stage of chronic kidney disease was defined according to the Kidney Disease Outcomes Quality Initiative classification. In patients that required haemodialysis, eGFR was arbitrarily set at zero.

Data were collected at 1, 3, 6 and 12 months after RTX use, at relapse and at the last follow-up.

Definitions
NS was defined as a syndrome comprising albuminemia <30 g/L and high-range proteinuria (uPr/Cr >3 g/g). Steroid-resistant NS was defined as persistent NS after 12 weeks of daily steroid intake at 1 mg/kg/day (maximum dose: 80 mg/day) followed by three pulses of intravenous steroids (1 g each). Relapse was defined as a urine dipstick of >3+ or recurrence of NS. Complete remission was defined as a normal uPr/Cr ratio (uPr/Cr <0.3 g/g) and/or a negative urine dipstick for protein for at least 3 days. Partial remission was defined as uPr/Cr ratio of between 0.3 and 3 g/g, and a normal albumin plasma level.

A complete clinical response was defined as complete remission and withdrawal of all IS treatments. A partial clinical response was defined as complete remission and withdrawal of at least one IS drug. Other cases were considered as a failure of RTX. B-cell recovery was defined by a CD19+ lymphocyte count of >1 mm³. A relapse that occurred within 2 months after withdrawal of other IS drugs and in <3 months after RTX was also considered a failure of RTX.

After assessment of outcomes in the overall cohort, analyses were also conducted in two subgroups according to RTX use: withdrawal of IS therapies while in remission (Group 1: patients with steroid-dependent NS), or treatment of a relapse (Group 2: patients with frequently relapsing NS; i.e. ≥2 relapses observed over the last 6 months or ≥4 relapses observed over any 12-month period) or with contraindication to long-term steroids or CNIs use.

Statistical analyses
Data are shown as means ± SDs, medians (lower and upper extremes) and percentages, as appropriate. Differences in quantitative parameters between groups were tested with Student’s t-test or a non-parametric test, as appropriate. Differences between qualitative results were compared using Fischer’s exact test. Univariate survival analysis was performed using the log-rank test. Multivariate analysis of the patients’ responses was performed using Cox’s regression model. Variables that did not significantly affect survival were removed by a stepwise procedure according to a likelihood ratio. Predictive factors for a complete clinical response were determined using multivariate logistic regression. The factors associated with complete response in the univariate analysis (P ≤ 0.20) were included in a multivariable analysis with a forward stepwise selection procedure. In the first step, all variables associated with complete response by univariate analysis (P < 0.20) were entered into the model. Entered variables were dropped if they were no longer significant when other variables were added. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. Imputation of missing data was performed according to their respective medians in the corresponding group. For the multivariate analysis, we deleted observations that included more than three missing variables of interest (i.e. those that were introduced in the multivariate analysis). A difference was considered significant if the P-value was <0.05. Analysis was performed with a StatView statistical software package (SAS Institute Inc.).

RESULTS
Baseline characteristics
Clinical characteristics at baseline (start of RTX) are summarized in Table 1. Between March 2006 and September 2012, 41 patients with MCNS and receiving RTX were followed in the 11 renal units that participated in this study (Figure 1).

Forty-one patients were included in this study (male to female ratio: 30:11). NS developed at a median age of 6 years (0.8–67) and RTX had been given at a median age of 26 years ([15–83]; the median time between the onset of NS and RTX therapy was 17 years (0–29)). All patients, except one, received long-term steroid therapy before receiving RTX, and achieved at least one complete response. Three patients received RTX because of steroids contraindication related to severe bipolar disorder, including one individual who received RTX as a first-line therapy.

Before RTX therapy, 36 patients received CNIs for 8 ± 6 years [88%: cyclosporin-A (CsA) n = 33 and tacrolimus n = 3], and 24 of these had a relapse when CNIs were withdrawn. Twenty-four individuals received MMF (59%), which allowed steroid withdrawal or a decrease in steroid intake at 1 mg/kg/day (maximum dose: 80 mg/day) following withdrawal of other IS therapies while in remission (Group 1: patients with steroid-dependent NS), or treatment of a relapse (Group 2: patients with frequently relapsing NS; i.e. ≥2 relapses observed over the last 6 months or ≥4 relapses observed over any 12-month period) or with contraindication to long-term steroids or CNIs use.

Table 1. Clinical characteristics of 41 patients with MCNS and receiving RTX

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall cohort (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female ratio</td>
<td>2:7:1</td>
</tr>
<tr>
<td>MCNS history</td>
<td></td>
</tr>
<tr>
<td>Age at the onset (years)</td>
<td>6 (0.8–67)</td>
</tr>
<tr>
<td>Onset before 15 years old [n (%)]</td>
<td>28 (68%)</td>
</tr>
<tr>
<td>Steroid-dependent NS (Group 1)</td>
<td>20/41</td>
</tr>
<tr>
<td>Steroid-dependent NS (Group 2)*</td>
<td>21/41</td>
</tr>
<tr>
<td>Immunosuppressors received before RTX</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>40 (98%)</td>
</tr>
<tr>
<td>Steroid at baseline (mg/day)</td>
<td>10 (2.5–100)</td>
</tr>
<tr>
<td>CNI (CsA or tacrolimus)</td>
<td>36 (88%)</td>
</tr>
<tr>
<td>CNI dependency</td>
<td>24 (59%)</td>
</tr>
<tr>
<td>Duration of treatment (years)</td>
<td>8 ± 6</td>
</tr>
<tr>
<td>MMF</td>
<td>24 (59%)</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>20 (49%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>Characteristics at baseline (RTX)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>26 (15–83)</td>
</tr>
<tr>
<td>Time from the onset of MCNS (years)</td>
<td>17 (0–29)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>92 ± 26</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>93 ± 25</td>
</tr>
<tr>
<td>NS [n (%)]</td>
<td>21 (51%)</td>
</tr>
</tbody>
</table>

CNIs, calcineurin inhibitors; CsA, cyclosporin-A; MMF, mycophenolate mofetil.
*Individuals with contraindication to long-term use of steroids or calcineurin inhibitors were also included in this subgroup.
24 patients received alkylating agents \((n = 20)\), levamisole \((n = 7)\) or azathioprine \((n = 5)\).

Before RTX therapy, 25 patients (63%) had steroid-related complications (hypertension, growth restriction, osteoporosis, obesity, diabetes or cataracts) and 24 had CNI-related complications (64%; nephropathy \(n = 20\)).

At baseline, mean serum creatinine and eGFR were 92 ± 26 \(\mu\)mol/L and 93 ± 25 mL/min/1.73 m\(^2\), respectively. uPr/Cr ratio was 1.3 g/g (0–23.0) and serum albumin was 32 ± 9 g/L. Twenty-one patients (51%) had NS.

**RTX regimen and early outcomes**

Dosage of RTX varied between patients: 21 received 1 g on Days 1 and 15; 12 received four weekly infusions (375 mg/m\(^2\)); one received 1 g once; five received two weekly infusions of 375 mg/m\(^2\); and two received three weekly infusions of 375 mg/m\(^2\). In all tested patients, complete B-cell depletion was obtained at 1 month after the last infusion of RTX. Nine patients received a second course of RTX when CD19\(^+\) B cells reappeared. In all patients, RTX infusions were preceded by an intravenous methylprednisolone bolus (2 mg/kg), acetaminophen (1 g) and hydroxyzine (50 mg), as recommended.

The clinical responses are shown in Figure 1. An overall complete clinical response was obtained in 25 patients (61%) and a partial response in seven (17%). Nine patients (22%) did not respond to RTX (Table 2).

In 20 of the 41 patients, RTX was given so that ISs could be stopped during remission (Group 1). Before RTX, all individuals of this group had received steroids [median dose: 10 mg/day (2.5–100)], 13 had received CNIs [65%; CsA \(n = 9\), median dose 2.7 mg/kg/day (1.9–5.6)] and seven had received MMF (35%). ISs used concomitantly to RTX are summarized in Table 2. Twelve patients (60%) were able to stop ISs: steroids after a median time of 6 months [1–30], after 4 months for CNIs [0–19] and after 0.5 month for MMF [0–36]. In five patients, CNIs and MMF were stopped, but NS relapsed while tapering steroids (partial clinical response). In three patients (15%), RTX failed to prevent a relapse of NS during steroid tapering (treatment failure).

In the remaining 21 patients, RTX was given during a relapse of NS in order to avoid toxicity from ISs (Group 2). In three of these 21 patients, RTX was given without another IS agent. In Group 2, 17 patients received steroids (94%), 8 received CNIs (44%) and 4 received MMF (22%). Thirteen patients (62%) achieved a complete clinical response [median time 32 days (15–90)], including the three patients who received RTX alone [median time 60 days (30–75)]. A partial clinical response was obtained in two patients (11%). In one of these, RTX reinfusion led to a subsequent complete clinical response. Finally, six patients (33%) did not respond to RTX: relapse during tapering of steroids and CNIs \((n = 3)\), relapse during continuous use of steroids, CNI and MMF \((n = 1)\) and persistent NS.

**Predictive factors for a complete clinical response**

In univariate analyses, the use of RTX in patients with ongoing MMF therapy was the only factor significantly associated with the lack of a complete clinical response (Table 3). The use of CNIs and MMF before RTX therapy, the concomitant use of steroids and RTX were also associated with a response to RTX, but significance was not reached \((P \leq 0.10)\). Because disease status (NS versus clinical remission) could be associated with a response to RTX, [17] this factor was also tested for, but was not predictive of treatment failure. In multivariate analyses, the use of RTX in patients already receiving MMF therapy was the only factor among the five listed that was significantly associated with the lack of a complete clinical response [OR 0.07, 95% CI (0.01–0.04), \(P = 0.003\)].

**Long-term outcomes**

Among the 41 individuals included in this cohort [median follow-up 44 months (6–82)], 32 (78%) had a complete
A relapse occurred in 18 patients (56%) after a median time of 18 months [3–36] (Table 4, Figure 2A). At relapse, 12 patients had NS and 6 had non-nephrotic proteinuria.

CD19+ B-cell recovery preceded a relapse [median time 2 months (0–14)] in 16 individuals (89%). However, in 9 of the 16 patients, relapse occurred 14 months (7–30) after CD19+ B-cell recovery. Neither NS at baseline nor the RTX regimen predicted relapse-free survival (Figure 2B–C).

All patients that relapsed after a complete clinical response (n = 13) received a second course of RTX: alone (n = 4), with a short course of steroids (n = 8) or with a short course of both CNIs and steroids (n = 1). All obtained a complete clinical response (median time 34 days [0–70]).

Among the five patients that relapsed after a partial clinical response, four received a second course of RTX with steroids (1 mg/kg/day) and obtained a partial clinical response; one of these five received steroids alone (1 mg/kg/day). None achieved a complete clinical response.

At the last follow-up [39 months after the first infusion (6–71) and 18 months after the last infusion (1–58)], all patients that had obtained a complete clinical response after the first RTX infusion still had complete remission at the end of follow-up.

**Tolerance to RTX**

No severe adverse events occurred after RTX therapy. Two patients had mild dyspnoea soon after infusion but no further complications. One patient had transient thoracic pain with mildly elevated serum-troponin levels during the first infusion, but with no recurrence during the second infusion. Two patients developed urinary tract infections that did not require hospitalization. No patient developed neutropenia (<500 mm3). No patient received routine prophylaxis (cotrimoxazole), but none developed pneumocystis infection.

**DISCUSSION**

In this study, we show that 61% of patients with steroid-dependent MCNS had a very good response to RTX
Table 4. Characteristics at relapse and response to treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 32)</th>
<th>Complete (n = 25)</th>
<th>Partial (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>18 (56%)</td>
<td>13 (52%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>Time to relapse (months)</td>
<td>18 (3–36)</td>
<td>21 (9–36)</td>
<td>8 (6–18)</td>
</tr>
<tr>
<td>Characteristics at relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>12</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Proteinuria &lt; 3 g/day</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>CD19+ B-cells recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16/18</td>
<td>13/13</td>
<td>3/5</td>
</tr>
<tr>
<td>CD-19 count (mm$^3$)</td>
<td>117 (0–641)</td>
<td>267 (21–641)</td>
<td>70 (0–133)</td>
</tr>
<tr>
<td>Time to relapse (months)</td>
<td>–</td>
<td>4 (0–14)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>IS regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>3</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Daily dose (mg/day)</td>
<td>2.5 (2.5–12.5)</td>
<td>–</td>
<td>2.5 (2.5–12.5)</td>
</tr>
<tr>
<td>CNI</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>MMF</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Treatment of relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTX</td>
<td>17 (94%)</td>
<td>13 (100%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>12 (67%)</td>
<td>8 (62%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>CNIs</td>
<td>1 (6%)</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>MMF</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>17/18</td>
<td>13/13 (CCR)</td>
<td>4/5 (PCR)</td>
</tr>
</tbody>
</table>

IS, immunosuppressors; CNI, calcineurin inhibitors; MMF, mycophenolate mofetil; CCR, complete clinical response; PCR, partial clinical response.

**FIGURE 2:** Relapse-free survival in the overall cohort (A) and according to the NS status at the time of RTX (B) or to the RTX scheme (C). NS, nephrotic syndrome.
(remission of NS and withdrawal of all ISs) and 78% had a clinical response.

The natural history of MCNS is highly heterogeneous and various IS regimens are used to avoid the long-term use of steroids. Despite the extensive literature on MCNS treatment, no consensus criteria on the response to treatments have emerged. In addition, most studies have included patients with mixed causes of NS (MCNS or FSGS), or with various responses to steroids (i.e. steroid dependency to steroid resistance). Hence, in published studies, a complete clinical response has been reported in 25–83% of patients according to age at diagnosis, criteria of response and renal pathology. Overall, no definitive conclusion can be drawn from these studies. Herein, we have used highly selective criteria for a complete clinical response in order to assess the ability of RTX to treat MCNS and to prevent a relapse.

Does RTX fulfill the criteria for efficacy in MCNS patients? In a cohort of 22 children with biopsy-proven MCNS, one or more IS drugs needed before RTX infusion could be withdrawn in 19 children (86%) following RTX therapy, but only 5 were free of all ISs. In a large multicentric international cohort of 57 patients (54 children) with steroids resistant (SRNS) or steroids dependent (SDNS) NS (MCNS or focal and segmental glomerulosclerosis), RTX led to a 95% reduction in relapse frequency in SDNS patients and to complete or partial remission in 16 of 33 (50%) of SRNS patients [18]. In 2011, Ravani et al. [19] showed that RTX, with low-dose steroids and CsA, was not inferior to a combination of higher doses of steroids and CsA in obtaining a complete clinical response. More recently, results from a cohort of 18 children who received RTX for a steroid-dependent MCNS, showed that RTX led to sustained remission in 22% of patients. At the end of the follow-up, ~45% of the patients were free of ISs [9]. In addition, in a recent cohort of 17 adult patients with MCNS, 12 patients (70%) achieved complete remission and 11 (67%) had not relapsed after a mean follow-up of 26.7 months [16]. Two additional prospective or retrospective studies, totaling 36 patients, showed that RTX allowed the discontinuation or minimization of steroids in 70–81% of adult patients [14, 20]. In our large cohort of 41 adult patients with a long history of relapsing MCNS and prolonged immunosuppression, RTX was beneficial in 78%, despite our stringent criteria.

Overall, our study and the literature suggest a trend towards RTX providing greater efficacy in treating MCNS in adulthood compared with childhood. The better efficacy in adults could be due to the inclusion, in paediatric series, of some cases of NSs of unrecognized genetic origin, that are, by nature, less sensitive to immunosuppressive treatment. In our study, we selected patients with a high probability of an underlying immune mechanism: steroid sensitivity, biopsy-proven MCNS, adult patients and no family history of renal disease. Because remission was prolonged for 12 months or more in most patients, RTX could thus be considered an effective treatment in this subset of patients.

Our cohort is the largest reported so far to assess the efficacy of RTX to treat MCNS in adulthood. Unfortunately, we failed to identify strong predictor factors for a response to treatment. The use of RTX plus on-going MMF treatment was associated with a lack of a complete clinical response. Because MMF acts through the blockade of B-cell activation and proliferation, patients that received RTX and MMF may have had MCNS that was partly or entirely independent of B cells and, thus, refractory to subsequent B-cell depletion. However, a response to MMF therapy before the addition of RTX was not predictive of treatment failure in our cohort. In the future, deciphering the role of B cells in the pathogenesis of MCNS could help us to predict the response to RTX. Indeed, a study recently suggested that RTX might have direct anti-proteinuric effect by remodelling the podocyte cytoskeleton [21]. Thus, whether RTX does act through B-cell depletion or podocyte cytoskeleton re-organization in MCNS needs further clarification.

In the last years, a Th17/T reg T-cell imbalance was associated with MCNS in children and adult patients (ref). Interestingly, Van de Veerdonk et al. showed that RTX-induced B-cell depletion reduces Th17 response in patients with rheumatoid arthritis. These preliminary findings, which confirm the interplay between T- and B-cells immunobiology, give a molecular rationale to the use of RTX in MCNS.

Whether prophylactic periodic re-injection of RTX (maintenance) should be proposed to patients with a complete clinical response remains a matter of debate. Tellier et al. [9] have suggested that this maintenance therapy may decrease relapses of NS. This finding has been confirmed in a large paediatric cohort of 46 children [10]. However, our data show that a relapse may occur a long time after B-cell recovery in some patients, and that almost all patients achieved a complete clinical response when RTX was resumed after a relapse. On the other hand, two patients relapsed with no detectable circulating CD19+ B cells in the peripheral blood, a finding that might be related to the escape of some intra-organ B cells to RTX-induced apoptosis, and the subsequent persistence of B cells in specific body compartments [22]. Hence, further studies need to compare prophylactic and curative strategies in terms of benefit-risk, as well as benefit-cost balances.

Additional uncertainties need clarification. The protocols for RTX infusion vary between centres (e.g. 1 g on Days 1 and 15, or four weekly infusions of 375 mg/m² each), but some preliminary studies suggest that a single 375 mg/m² dose may induce long-term remission of NS and allow steroid withdrawal [15,23–25]. However, in a German registry, the duration of remission of patients receiving one or two infusions of RTX (375 mg/m²) was significantly shorter than in those receiving three or four infusions (10.3 ± 3.5 months versus 23.3 ± 18.7 months) [11]. Recently, Takei et al. [26] suggested that a single dose of RTX 375 mg/m² administered at baseline and at Month 6 may be a safe and efficient alternative in adult patients with MCNS. In our cohort, various regimens of RTX were used, but no definitive conclusion could be made because of the small size of the subgroups.

It is also not known whether complete remission should be obtained (with the help of high-dose steroids) before RTX infusion, in order to avoid excessive loss of urinary RTX [15,17]. In our study, remission of NS was not a prerequisite before RTX therapy. Among the 21 patients that had NS at baseline, 18 achieved a complete clinical response, including three that did not receive concomitant steroids. Thus, our findings highly suggest that RTX alone may be sufficient to induce remission in adulthood.
Finally, tolerance to RTX was excellent in our cohort. Despite the long-term use of ISs in most patients, no severe infections or neoplasms occurred after the prolonged follow-up. In contrast to previous studies [27], no patient developed opportunistic infection, such as Pneumocystis carinii or JC-virus-related progressive multifocal leukoencephalopathy.

To overcome the limitations due to the retrospective character of our study and heterogeneity in the RTX and steroid regimens, we used stringent criteria to determine a complete response. We obtained a high rate of complete clinical response (61%), despite the high level of steroid requirements at baseline, which indubitably suggests a beneficial effect of RTX in patients with steroid and/or CNI-dependent MCNS. However, these limitations preclude drawing practical guidelines and urge to perform a large-scale randomized controlled trial including adult patients.

In summary, RTX led to a significant and sustained clinical response in most adult patients with a minimal change NS. Future studies will need to identify subsets of patients that may benefit from RTX as a first line, as well as to define optimal regimens for both initial and subsequent RTX cures.

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CONFLICT OF INTEREST STATEMENT

None declared.

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