Frequent-relapsing, steroid-dependent minimal change disease: is rituximab the answer?

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Keywords: minimal change disease, nephrotic syndrome, relapses, rituximab, steroid

In patients with minimal change disease, development of steroid-dependency or frequent relapses pose difficult therapeutic problems. Prolonged administration of corticosteroids or the use of additional immunosuppressive therapy can result in significant toxicity. Recent data point to the use of rituximab as an important treatment option to induce long-term remission in patients with minimal change diseases who are either frequent relapers or require significant immunosuppression to remain in remission.

Minimal change disease (MCD) accounts for the majority of cases of idiopathic nephrotic syndrome (NS) in children and up to 20% of cases of idiopathic NS in white adults [1]. On kidney biopsy, MCD is characterized by widespread effacement of epithelial cell foot processes on electron microscopy, while glomeruli appear normal on light microscopy and immunoglobulin and complement deposition are absent on immunofluorescence. Most cases of MCD are idiopathic, although drugs (such as non-steroidal anti-inflammatory drugs), hematological malignancies (mainly Hodgkin lymphoma) and thymoma are well-recognized causes of secondary MCD. While most patients respond to corticosteroid therapy, up to 25% of treated patients have frequent relapses and up to 30% of patients become steroid dependent [2, 3]. In these patients, alternative therapies aimed at minimizing corticosteroid toxicity have been used, including alkylating agents, antimetabolites and calcineurin inhibitors. While these agents may be beneficial, some patients respond poorly or not at all, and their use may be complicated by the development of serious adverse effects, e.g., infertility and malignancy with the use of cyclophosphamide. With calcineurin inhibitors, steroid dependency may be replaced by dependence on calcineurin inhibitors, requiring years of treatment and the associated risk of nephrotoxicity [3]. In some patients, these agents are used in combination, adding to the potential adverse effects. An additional problem is non-compliance, especially in young patients. As such, alternative therapies that can result in the induction of long-term remission with a favorable safety profile have been sought.

Rituximab (RTX), a chimeric monoclonal antibody directed against the B-lymphocyte-restricted cell-surface protein CD20, has achieved great success in the treatment of a number of autoimmune conditions affecting the kidney, including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and membranous nephropathy [4]. The serendipitous findings that RTX treatment in two young patients—a 16-year-old patient with severe idiopathic thrombocytopenic purpura and steroid-dependent NS with multiple relapses [5] and a child with recurrent focal segmental glomerulosclerosis (FSGS) after undergoing kidney transplantation who developed a lymphoproliferative disease—resulted in remission of proteinuria [6] suggested that B cells may be involved in the pathogenesis of FSGS and NS. Considering that MCD can evolve into FSGS and both have podocyte injury and widespread foot process effacement as a common denominator, it is not surprising that a ‘leap of faith’ could be made in using RTX to treat MCD (Figure 1).

Indeed, two case reports—one by Gilbert et al. [7] of a 15-year-old girl with high-dose steroid-dependent MCD and one by Francois et al. of a 22-year-old woman with multirelapsing MCD—showed that RTX was effective in inducing complete remission of NS. The case reported by François et al. [8] is illustrative, for the patient had a history of MCD since she was 6 years old, with multiple relapses requiring repeated courses of cyclophosphamide, prolonged cyclosporine exposure with the development of nephrotoxicity, and unresponsiveness to mycophenolate mofetil and to an anti-CD25 antibody (basiliximab). She was treated with RTX, 375 mg/m², weekly for 4 weeks, with retreatment at 1 year. Complete remission 3 weeks later persisted for up to 28 months despite the absence of maintenance immunosuppression.
Since then, several case reports, retrospective series and prospective studies [9–24] have shown that RTX is capable of inducing sustained remission of NS together with marked reduction or discontinuation of corticosteroids and/or immunosuppressive (IS) drugs in patients—both children and adults—with MCD who were steroid dependent or had frequent relapses (Tables 1 and 2). It has shown efficacy when given to patients in complete remission or while nephrotic [19]. Patients with steroid resistant but cyclosporine-sensitive NS also responded to RTX [10]. A few patients with steroid-resistant NS also responded to RTX [11, 12, 25].

In the current issue of *NDT*, Bruchfeld et al. [26] report on the long-term follow-up of 16 patients (9 women, 7 men; aged 19–73 years) with frequent-relapsing, steroid-dependent or steroid-resistant, biopsy-proven MCD treated with RTX. Patients had been treated with corticosteroids and/or IS therapy (cyclophosphamide, calcineurin inhibitors, azathioprine, mycophenolate mofetil, chlorambucil, levamisole) but despite that had experienced 3 to >20 relapses. The majority were nephrotic or near nephrotic before RTX treatment. Thirteen patients (81%) responded to therapy with complete remission. Two patients had a 50 and 70% reduction in proteinuria. One patient did not respond. Average follow-up was 38 months. Seven relapses occurred after 9–28 months. Relapses occurred at the time of B-cell recovery, but not all patients relapsed after B-cell reconstitution. Four were retreated with RTX and went back into remission. In three patients, relapses were minor and responded to a reduced dose of corticosteroids. Adverse events were minor and infusion related. At the latest follow-up, 66% of the patients who responded to RTX were no longer on any maintenance IS therapy. The study represents not only one of the largest in adults, but also one with the longest follow-up. It confirms that RTX can induce prolonged remission in patients whose disease is difficult to control. But how does RTX do it?

The pathogenesis of MCD is unknown. In 1974, Shalhoub [27] proposed that MCD was due to a systemic abnormality of T-cell function. This hypothesis was supported by a number of clinical observations: (i) the lack of evidence for an antibody response; (ii) remission induced by measles, which modifies cell-mediated immunity; (iii) association with atopy or acute allergies (e.g. bee sting) and infections; (iv) association with Hodgkin lymphoma and (v) therapeutic benefit of corticosteroids and cyclophosphamide. Observations that infusion of supernatants of T lymphocytes from patients with MCD induced proteinuria in rats added to the suggestion of a circulating chemical mediator toxic to the podocyte [28]. Further support comes from the association of MCD with thymoma [29] and by the patient’s response to cyclosporine, which disrupts T-cell activation by inhibiting IL-2 production. However, extensive research has failed to characterize the putative vascular permeability factor(s).

More recently, a number of clinical and immunological findings suggest that B cells are also involved in MCD. Increased levels of both the soluble, low-affinity IgE receptor CD23 (a marker of B-cell activation) and the soluble IL-2

![Figure 1: Top panel: Minimal change disease. (A) Light microscopy showing normal appearing glomerulus (Periodic acid Schiff stain, x40). (B) Electron microscopy showing diffuse effacement of foot processes (x2500). Bottom panel: Tip lesion, focal segmental glomerulosclerosis. (C) Segmental sclerosis at tubular pole with adhesion of few capillary loops to Bowman’s capsule (Trichrome stain). Note protein reabsorption granules (x60). (D) Electron microscopy showing diffuse effacement of foot processes (x2500). Black arrow points at tip lesion, white arrows point at diffuse effacement of foot processes.](image-url)
Table 1. Use of rituximab in children with steroid-dependent or frequent-relapsing minimal change disease

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Age, mean ± SD, Sex</th>
<th>Time from diagnosis to RTX, years</th>
<th>Maintenance immunosuppression at end of follow-up</th>
<th>Outcome</th>
<th>Relapses</th>
<th>Follow-up, months</th>
<th>RTX dose</th>
<th>Follow-up, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert et al. [7]</td>
<td>1</td>
<td>15 F</td>
<td>1</td>
<td>CR</td>
<td>18</td>
<td>375 mg/m² × 4</td>
<td>375 mg/m²</td>
<td>13.5</td>
<td>375 mg/m² × 4</td>
</tr>
<tr>
<td>Smith [22]</td>
<td>1</td>
<td>14 M</td>
<td>1</td>
<td>CR</td>
<td>10</td>
<td>375 mg/m² × 1</td>
<td>375 mg/m²</td>
<td>11</td>
<td>375 mg/m² × 1</td>
</tr>
<tr>
<td>Guigonis et al. [10]a</td>
<td>2</td>
<td>2.2 14.3</td>
<td>1</td>
<td>NR</td>
<td>3</td>
<td>375 mg/m² × 2</td>
<td>375 mg/m²</td>
<td>13 M</td>
<td>375 mg/m² × 2</td>
</tr>
<tr>
<td>Kemper et al. [21]</td>
<td>37</td>
<td>134.5 ± 12.8</td>
<td>9 M, 25 M, 10.5</td>
<td>CR</td>
<td>36</td>
<td>375 mg/m² × 1.4</td>
<td>284 mg/d</td>
<td>5 M, 5.5 ± 0.3</td>
<td>36</td>
</tr>
<tr>
<td>Fujinaga et al. [15]</td>
<td>10</td>
<td>11.1 ± 4.5</td>
<td>9 F, 1 F</td>
<td>CR</td>
<td>36</td>
<td>375 mg/m² × 1</td>
<td>375 mg/m²</td>
<td>5 M, 5.5 ± 0.3</td>
<td>9 F</td>
</tr>
<tr>
<td>Kamei et al. [15]</td>
<td>16</td>
<td>11.1 ± 4.5</td>
<td>11 F</td>
<td>CR</td>
<td>36</td>
<td>375 mg/m² × 1</td>
<td>375 mg/m²</td>
<td>5 M, 5.5 ± 0.3</td>
<td>11 F</td>
</tr>
<tr>
<td>Sellier-Leclerc et al. [16]</td>
<td>17</td>
<td>12.9 ± 0.7</td>
<td>9 F</td>
<td>CR</td>
<td>36</td>
<td>375 mg/m² × 1</td>
<td>375 mg/m²</td>
<td>9 F, 9.5</td>
<td>375 mg/m² × 1</td>
</tr>
<tr>
<td>Ravioli et al. [20]b</td>
<td>20</td>
<td>9.9 ± 4.3</td>
<td>16 F</td>
<td>CR</td>
<td>36</td>
<td>375 mg/m² × 1</td>
<td>375 mg/m²</td>
<td>16 F</td>
<td>375 mg/m² × 1</td>
</tr>
</tbody>
</table>

aThree FSGS and Three unknown.

B cells may be involved in the pathogenesis of the disease. The fact that patients with B-cell-related autoimmune diseases, such as systemic lupus erythematosus (SLE), may develop MCD further supports this concept, but mechanistic studies are needed. It should also be remembered that cyclophosphamide has striking effects on B-cell function and suppresses the secretion of immunoglobulins.

However, a role for T cells cannot be dismissed because RTX may affect T-cell function. RTX has been effective in the treatment of rheumatoid arthritis, a classic T-cell-mediated disease. In patients with SLE, treatment with RTX results in a decrease in activated T cells [31], although the effect may be disease specific since no such changes were documented in patients with membranous nephropathy treated with RTX [32]. Furthermore, a small population of T cells do express CD20 [33]. Alterations in the nuclear factor kappa B (NF-kB) pathway of both CD4 T cells and non-CD4 mononuclear cells may be involved in the development of MCD [34]. RTX inhibits the constitutive NF-kB signaling pathway in B-cell lines, and it is possible that inhibition of this pathway may be beneficial in NS. B cells also play an important role in induction of inflammatory cytokines, antigen presentation to T cells, dendritic cells, and macrophages, T-cell activation and generation of ectopic lymphogenesis [35], and RTX may directly or indirectly alter T-cell function in patients with MCD. In fact, as Shalhoub [27] pointed out, ‘It is conceivable that the feedback control system governing the activity of helper and suppressor T cells depends to some extent on the concentration of specific immunoglobulin whose synthesis is affected by these cells. Consequently, if abnormalities of Ig synthesis can be demonstrated in lipoid nephrosis, the primary disturbance may involve B-cell dysfunction.’

More recently, increased expression of CD80 on podocytes has been associated with the development of proteinuria (as reviewed by Ishimoto et al. [36]). CD80 is expressed on antigen-presenting cells, natural killer cells and B cells and provides a costimulatory signal for T cells by binding to the T-cell receptor CD28. It is postulated that in patients with MCD, a foreign antigen and/or T cell cytokines lead to induction of CD80 by the podocyte. Impaired down-regulation of CD80 expression, due to an inadequate CTLA-4 response by circulating regulatory T cells, would result in persistent CD80 expression, and foot process fusion, leading to the development of proteinuria.

It is also possible that, similar to that reported for cyclosporine, RTX may exert antiproteinuric effects by modulating podocyte function. A recent study by FORNONI et al. [37] showed that serum from patients with recurrent FSGS induced a decrease in human podocyte sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) protein and acid sphingomyelinase (ASMase) activity. These sphingolipid-related proteins are important in receptor organization and molecular signaling in receptor CD25 (a marker of T-cell activation) have been found during proteinuria relapses in patients with steroid-sensitive NS [30]. The CD23 receptor is a marker of B-cell activation and proliferation and appears to be under the control of T cells. The fact that RTX has been able to induce sustained remission in a number of patients with MCD suggests that B cells may be involved in the pathogenesis of the disease. The fact that patients with B-cell-related autoimmune diseases, such as systemic lupus erythematosus (SLE), may develop MCD further supports this concept, but mechanistic studies are needed. It should also be remembered that cyclophosphamide has striking effects on B-cell function and suppresses the secretion of immunoglobulins.
Table 2. Summary of use of rituximab in adults with steroid-dependent or frequent-relapsing minimal change disease

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Age, mean ± SD, years</th>
<th>Sex</th>
<th>Time from RTX dose to follow-up, months</th>
<th>Outcome</th>
<th>Relapses</th>
<th>Maintenance immunosuppression at end of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francois et al. [8]</td>
<td>1</td>
<td>23 ± 7</td>
<td>F</td>
<td>1 year</td>
<td>CR</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Yang et al. [11]</td>
<td>1</td>
<td>41 ± 7.2</td>
<td>M</td>
<td>8 months</td>
<td>PR</td>
<td>0</td>
<td>Pred, 7.5 mg/day</td>
</tr>
<tr>
<td>Corron et al. [13]</td>
<td>1</td>
<td>23 ± 7</td>
<td>M</td>
<td>3 months</td>
<td>CR</td>
<td>0</td>
<td>MMF, 250 mg twice daily; Pred, 5 mg/day</td>
</tr>
<tr>
<td>Hofstra et al. [9]</td>
<td>1</td>
<td>20 ± 6.3</td>
<td>F</td>
<td>18 months</td>
<td>CR</td>
<td>0</td>
<td>Pred, 7.5 mg/day</td>
</tr>
<tr>
<td>Yang et al. [11]</td>
<td>1</td>
<td>41 ± 7.2</td>
<td>F</td>
<td>8 months</td>
<td>PR</td>
<td>0</td>
<td>Pred, 7.5 mg/day</td>
</tr>
<tr>
<td>Korusu et al. [14]</td>
<td>1</td>
<td>23 ± 7</td>
<td>M</td>
<td>3 months</td>
<td>CR</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Korusu et al. [14]</td>
<td>1</td>
<td>23 ± 7</td>
<td>M</td>
<td>3 months</td>
<td>CR</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>Takei et al. [19]</td>
<td>25</td>
<td>30 ± 12</td>
<td>M,F</td>
<td>10 months</td>
<td>CR</td>
<td>0</td>
<td>MMF, 5 mg twice daily; Pred, 5 mg/day</td>
</tr>
<tr>
<td>Munyentwali et al. [24]</td>
<td>17</td>
<td>29 ± 12</td>
<td>M,F</td>
<td>10 months</td>
<td>CR</td>
<td>0</td>
<td>MMF, 5 mg twice daily; Pred, 5 mg/day</td>
</tr>
</tbody>
</table>

CR = complete remission; PR = partial remission; Pred = prednisone; RTX = rituximab; SD = standard deviation.

The adverse effect profile of RTX has been remarkably good, mainly involving mild infusion reactions, transient hypotension or hypertension, and rashes, which can be minimized by pretreatment and by slowing the infusion rate. Hypogammaglobulinemia may also occur but is not associated with an increased risk of infection [10]. However, Pneumocystis jirovei pneumonia has been reported complicating RTX therapy, and prophylaxis is recommended while patients are B-cell depleted [10]. Progressive multifocal leukoencephalopathy (PML), a fatal neurological condition characterized by severe demyelination due to the JC virus, has been reported in two patients with MCD treated with RTX, which led to a box warning from the US Food and Drug Administration. However, >24 cases of PML...
have been reported in patients with SLE and ANCA-associated vasculitis who never received RTX [38]. No case of PML has been reported in patients with NS treated with RTX, or RTX used as monotherapy. Although small, patients should be informed of the potential risk of PML before initiating RTX treatment. But would the adverse effect profile remain the same once patients are exposed to repeated courses of RTX? This is of concern because many patients relapse within the first 6–12 months after RTX and may undergo retreatment. In other words, what would be the consequences of converting patients from a steroid or calcineurin inhibitor dependence to RTX dependence?

The available data indicate that RTX is a new therapeutic option in the treatment of patients with MCD. Recent Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines suggest that RTX be considered in children who are steroid-dependent or frequent relapsers despite optimal maintenance therapy and/or have severe immunosuppression adverse effects [39]. Although not stated in KDIGO, the same recommendations could be made regarding treatment in adults. Additional prospective controlled studies and long-term follow-up are needed to confirm the efficacy and safety of RTX in the treatment of patients with MCD.

ACKNOWLEDGEMENTS

F.C.F. and S.S would like to thank the Fulk Family Foundation for its research support.

CONFLICT OF INTEREST STATEMENT

F.C.F. has received unrestricted research grants from Genentech, Inc., the manufacturer of rituximab.


REFERENCES

Fistula-first and catheter-last: fading certainties and growing doubts

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Keywords: Arteriovenous fistula, Central venous, catheters, Haemodialysis, Vascular access

In this issue of Nephrology Dialysis and Transplantation, Grubbs et al. [1] present USRDS data on the association between vascular access type at hemodialysis initiation and 6-month mortality in 117,277 patients who started hemodialysis therapy between January 2005 and December 2007. Thanks to additional access information included in the End-Stage Renal Disease Medical Evidence Report (form CMS-2728) since 2005 [2], the authors were able to classify the initial hemodialysis access as either fistula alone, graft alone, catheter with maturing fistula, catheter with maturing graft or catheter alone. The authors found that, compared with people using a fistula, the risk of death from all causes was progressively higher in people using grafts, in those using catheters with a maturing fistula, in those using catheters with a maturing graft and in those using catheter without a maturing arteriovenous access. Six-month mortality data were similar to long-term results from a previous analysis of USRDS data [3].

Grubbs et al. [1] also reported that the relative risk of death associated with the use of catheters alone versus fistulas alone was 1.95 in unadjusted analysis, 1.69 after standard adjustment and 1.54 in a fully adjusted analysis that included information on patient health status. Although the attenuation of the strength of the association between access type and mortality was larger from unadjusted analysis to an analysis controlled for standard confounders (21% on a log-scale), inclusion of health status in the adjusted model further decreased the relative risk (by 18%). Of note, the authors found that the probability of limited functional status (i.e. institutionalization, inability to ambulate or transfer, or assistance required for the activities of daily living) was progressively higher in those using grafts (18.8%) and catheters with (23.5%) or without a maturing arteriovenous access (25.5%) compared with people using fistulas alone (18.0%).

In FOCUS

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