

# NEPHROLOGY

# Rounds®

## Minimal Change Disease

By DANIEL J. BECKER, MD, PhD

Minimal change disease (MCD) is a common cause of nephrotic syndrome in children, but is less prevalent in adult patients. Light microscopy of the glomerulus usually appears normal in MCD, whereas electron microscopy demonstrates effacement of podocyte foot processes. The pathogenesis of MCD is not well-defined, although there is evidence that T lymphocytes play a role, perhaps via the secretion of a "permeability factor" into the circulation. Corticosteroids are first-line therapy for MCD and are effective in most patients. Additional immune-modulating agents are also used in those patients who are resistant to and/or dependent on corticosteroid therapy. This issue of *Nephrology Rounds* reviews recent advances in our understanding of the pathogenesis and treatment of adult MCD.

### Background

MCD is a glomerular disorder that typically leads to the sudden onset of nephrotic-range proteinuria. Affected individuals express additional features of the nephrotic syndrome (NS), including edema of the extremities and face, hypoalbuminemia, and hyperlipidemia. Minimal changes are seen on light and immunofluorescence microscopy of renal-biopsy specimens, an observation from which MCD derives its name. On electron microscopy, podocyte foot processes are effaced and retracted; this disrupts the filtration barrier of the glomerulus and provides the pathological correlate for the clinical finding of heavy albuminuria.<sup>1</sup>

MCD is the most common cause of NS in children, accounting for approximately 90% of cases in children aged <10 years and approximately 50% of cases in children >10 years.<sup>1,2</sup> As a result, young children with NS are usually presumed to have MCD and are treated empirically. Unless atypical features are present, most pediatric nephrologists reserve renal biopsy for children who are resistant to an initial course of corticosteroids. In contrast, MCD is the third most common variant of idiopathic NS in adults, after focal and segmental glomerulosclerosis (FSGS) and membranous nephropathy. Most case series report MCD in approximately 10%-15% of adults with idiopathic NS.<sup>3,4</sup> For this reason, unless contraindicated, most nondiabetic adults with NS should undergo renal biopsy to determine the underlying pathological lesion, especially if there is rapid onset of proteinuria and edema.

### Pathogenesis

In the majority of MCD cases, there is no identifiable etiology and the diagnosis is idiopathic or primary MCD. However, in a subset of MCD patients, underlying diseases or stimuli occur concurrently with the onset of NS and are thought to be involved in the pathological mechanism (Table 1). Neoplastic processes have frequently been reported in association with MCD, especially Hodgkin lymphoma and other hematopoietic neoplasms. Multiple medications have also been reported in association with MCD, most prominently nonsteroidal anti-inflammatory drugs (NSAIDs). Other possible MCD precipitants include a variety of infections and allergens.<sup>5</sup> Although coincidence does not prove causality, many cases of paraneoplastic MCD associated with Hodgkin lymphoma have been reported to remit upon successful oncological treatment and subsequently recur upon oncological recurrence.<sup>6</sup> Additionally, even in patients initially thought to have idiopathic MCD, careful history-taking at the time of NS recurrence will often reveal a potential trigger, such as a recent upper respiratory-tract infection and/or exposure to NSAIDs.

The relationship between MCD and primary FSGS is an active area of debate in nephrology. Podocyte injury with foot-process effacement is a central feature of both disorders, but segmental sclerosis of glomeruli is unique to FSGS.<sup>7</sup> Moreover, an initial biopsy in patients with episodic nephrotic proteinuria often leads to a diagnosis of MCD, but in some, it is later revised to FSGS after persistent proteinuria develops and sclerotic glomeruli are seen on repeat biopsy. Whether this represents disease progression or simply reflects sampling error on the initial biopsy is an open question. Nevertheless, some authors have proposed that MCD and FSGS comprise a spectrum of disease with MCD representing a milder, reversible injury to foot processes, whereas FSGS corresponds to more severe injury that ultimately leads to irreversible glomerular scar formation.<sup>8</sup>

Fueling the argument that MCD and FSGS are pathogenetically related are studies of patients with idiopathic NS who have received renal transplants. In 1972, Hoyer et al<sup>9</sup> described 3 young

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**Table 1: Conditions reported in association with minimal change disease**

• <b>Neoplasms</b>	
Hodgkin lymphoma	
Non-Hodgkin lymphoma	
Leukemia	
Solid tumors (multiple)	
• <b>Drugs</b>	
NSAIDs	Tamoxifen
Lithium	Antibiotics
Enalapril	(ampicillin, cefixime, etc.)
Interferon ( $\alpha, \gamma$ )	Immunizations
• <b>Infections</b>	
Syphilis	<i>Echinococcus</i>
HIV	<i>Ehrlichia</i>
<i>Mycoplasma</i>	
• <b>Allergic stimuli</b>	

NSAID = nonsteroidal anti-inflammatory drug;  
HIV = human immunodeficiency virus

Adapted from Glassock RJ. *Nephrol Dial Transplant*. 2003; 18(Suppl 6):vi52-58.

patients with steroid-resistant idiopathic NS; all 3 eventually progressed to renal failure and received renal transplants. Recurrent NS was diagnosed within months of transplantation in all three patients, and in one patient, nephrotic range proteinuria was noted on the first postoperative day. Biopsy specimens obtained shortly after the NS diagnosis, both before and after transplantation, demonstrated changes consistent with minimal change nephropathy; segmental sclerosis was absent or rare on light microscopy and no immune complexes were found on immunofluorescence. Subsequent renal biopsy specimens were obtained much later after the diagnosis of NS, both before and after transplantation, and demonstrated more prominent FSGS including segmental sclerosis in large numbers of glomeruli.

In addition to underlining the possible link between MCD and FSGS, the report of Hoyer et al,<sup>9</sup> as well as multiple subsequent case reports, established that patients with idiopathic NS were at risk for recurrence of NS post-transplantation, despite ongoing immunosuppression to prevent organ rejection. Thus, these reports suggest that MCD is a systemic disorder, possibly caused by a circulating factor in the serum, rather than a pathological entity restricted to the kidney. Further strengthening this view is a report describing a patient with relapsed MCD who developed an intracranial hemorrhage leading to brain death.<sup>10</sup> Despite active NS, his kidneys were transplanted into 2 recipients. Initially, both recipients had proteinuria of approximately 1-2 g/24 hours at 1 week post-transplantation (compared with 23g/24 hours in the donor prior to transplant), but subsequent measurements were all <1g/24 hours. Biopsies of the kidneys several weeks post-transplantation revealed acute tubular necrosis, but the podocyte foot processes appeared normal. In other words, the same kidneys that had been spilling massive amounts of protein prior to transplant subsequently developed normal glomerular function when transferred to another patient “environment;” this included a rapid repair of foot-process interdigitation and resolution of nephrotic proteinuria.

Based in part on early experiences with renal transplantation for MCD, in a seminal 1974 manuscript, Shalhoub<sup>11</sup>

proposed that MCD is caused by a disordered function of T lymphocytes. In addition to transplant data, Shalhoub tied together the association of MCD with Hodgkin disease, the therapeutic response to immune-suppressing medications (eg, steroids and cyclophosphamide), and the observation of MCD remission in response to measles, to hypothesize that MCD is related to a defect in cell-mediated immunity. He also postulated that MCD is due to a circulating factor produced by an abnormal clone of T cells directly increasing glomerular filtration barrier permeability. In the 35 years since this publication, there has been a substantial effort to identify the “permeability factor” responsible for MCD, but unfortunately it has yet to be discovered.<sup>8,12</sup>

Multiple lines of evidence have supported the existence of a permeability factor in MCD and/or FSGS. First, several studies have demonstrated that supernatants from T-cell hybridomas derived from patients with active NS can induce albuminuria and podocyte foot-process effacement when injected into rats; hybridoma supernatants from normal patients have no effect.<sup>13-15</sup> Moreover, using isolated rat glomeruli in an *in vitro* method for assessing albumin permeability, Savin and colleagues<sup>16</sup> examined the serum of 100 patients with FSGS; they found that serum from patients relapsing after transplantation induced substantially greater glomerular permeability than serum from patients with no post-transplantation recurrence or serum from normal patients. In addition, plasmapheresis in patients with recurrent FSGS reduced the ability of their serum to induce glomerular permeability.

The notion of MCD as a T-lymphocyte disorder can also be considered in the context of the hygiene hypothesis, which asserts that improved sanitation in Westernized nations has led to a decrease in chronic childhood infections and, in turn, led to a shift from a T helper 1 (Th1)-predominant immune phenotype towards a Th2-predominant response. The hygiene hypothesis was originally developed to explain an observed increase in Th2-dependent allergic conditions in Western societies over the past several decades. However, as Hurtado and Johnson have proposed,<sup>17</sup> the hygiene hypothesis might also inform our understanding of global trends in glomerulonephritis (GN) epidemiology. Whereas Th1-predominant membranoproliferative GN is the most common GN in many developing nations, MCD is substantially more common in many industrialized countries such as the United States (US), Japan, and Spain. This observation suggests that an immune imbalance favoring the Th2-phenotype increases the risk for developing MCD.

Numerous studies have attempted to determine if the levels of Th2-associated cytokines such as interleukin (IL)-4, IL-13, and interferon (IFN)- $\alpha$  in the serum of individuals with MCD correlate with relapse, but a convincing link to a single cytokine has yet to be established.<sup>18</sup> Other cytokines or secreted factors such as vascular endothelial growth factor, IL-8, and tumor necrosis factor- $\alpha$  have also been investigated, but again there has been no firm evidence implicating a single factor that correlates with active MCD. Recently, a mouse model of idiopathic NS was developed in which peripheral blood mononuclear cells from patients are injected into mice, thus allowing for engraftment and production of mature human lymphocytes in the mice. When CD34+ stem cells were excluded from the population of injected cells, the mice did not develop albuminuria, indicating a potential role for immature differentiating cells in the pathogenesis of MCD and FSGS.<sup>19</sup> Ultimately, a comprehensive understanding of

the molecular mechanism of MCD awaits additional data from this active field of research.

## Prognosis

The prognosis for MCD is excellent even in adults, who have slower responses and a substantially greater possibility of therapy resistance. The spontaneous remission rate of MCD in adults is difficult to judge due to limited data, but one early British study demonstrated remission of NS (defined by proteinuria <1 g/24 hours) in approximately 20% of untreated MCD patients at 6 months and nearly 65% at 2 years.<sup>20</sup> Therapy with corticosteroids dramatically improves the rate of remission, as well as the overall proportion of patients who eventually achieve remission. Although the rapidity of remission is less than in the pediatric population, 80%-90% or more of adult patients eventually achieve remission on corticosteroid therapy.<sup>21-24</sup>

Early aggressive therapy for MCD is indicated to reduce the risk of complications of NS, such as infections, accelerated atherogenesis due to hyperlipidemia, and thrombosis (Table 2).<sup>25</sup> Prior to routine therapy for NS, these complications were frequently fatal. Acute kidney injury (AKI) is a well-described but relatively uncommon complication of MCD. In most cases of MCD-associated AKI, pathological examination reveals tubular necrosis. Advanced age, NSAIDs, and hypovolemia appear to be risk factors for AKI in patients with MCD.<sup>25,26</sup> Renal function typically recovers after an episode of MCD-associated AKI, but it is not always complete.<sup>27</sup> Progression to end-stage renal disease rarely occurs and appears limited to patients who are resistant to corticosteroid therapy and/or who relapse frequently.<sup>28</sup>

## Initial therapy

### Corticosteroids

Corticosteroids are the mainstay of initial therapy of MCD in adult patients. However, most of the data on the efficacy of corticosteroids in MCD come from the pediatric literature.<sup>29,30</sup> The paucity of randomized controlled trials (RCTs) for MCD in adult patients was highlighted by a recent report from the Cochrane Collaboration.<sup>31</sup> Despite an exhaustive review of the literature on MCD therapy in adults, the authors identified only 3 RCTs that met their rigorous criteria; all 3 were completed over 20 years ago and were underpowered (the largest trial enrolled only 28 patients).

One of the earliest trials of corticosteroid therapy for NS was completed by Black and colleagues<sup>20</sup> in 1970, enrolling 125 adult patients with NS, including 31 patients with MCD, 19 patients with membranous nephropathy, and 75 patients in a heterogeneous group with proliferative GN. Patients were randomized to either treatment with prednisone at 20-30 mg daily for at least 6 months or no treatment. Unfortunately, results were only partially stratified according to biopsy findings, but their data indicated that approximately 65% of MCD patients in the treatment group achieved remission of proteinuria at 3 months compared to 0% in the control group. Over the course of the next 12 months, the rate of remission in the treatment group rose to approximately 90%, whereas the spontaneous remission rate in the control group was 50%. Based on the "early and dramatic" response to prednisone in the MCD group from this trial, corticosteroids became a *de facto* standard of care for adult MCD.<sup>31</sup> Although patients were recruited from multiple centers, all appeared to be from Great Britain, and it is therefore unclear whether the findings are widely applicable to other populations.

**Table 2: Complications of nephrotic syndrome**

• <b>Infections</b>
Peritonitis
Cellulitis
Sepsis
• <b>Thrombosis</b>
Deep extremity veins
Renal veins
Arterial (more common in children)
• <b>Acute kidney injury</b>
• <b>Accelerated atherogenesis</b>
• <b>Protein depletion</b>

Adapted from Cameron JS. *Am J Kidney Dis.* 1987;10(3):157-181.

Nevertheless, given the long experience with corticosteroid therapy for MCD, it would be difficult to undertake another placebo-controlled therapeutic trial for MCD.

The optimal dose and duration for initial corticosteroid therapy has not been rigorously established. An Italian study<sup>32</sup> of 89 patients (22 adults) aimed to determine if initial treatment of MCD with a 3-day course of intravenous (IV) methylprednisolone was superior to high-dose oral prednisone. Patients were randomized to either methylprednisolone at 20 mg/kg/day for 3 days followed by low-dose prednisone (0.5 mg/kg/day initially followed by tapered dose over 5 months) or high-dose prednisone at 1 mg/kg/day for 4 weeks followed by low-dose prednisone. In the adult patients, there was no difference in complete remission, maintenance of remission, or adverse events. Moreover, in a recent retrospective review of 95 adults with MCD, who had been referred to a single US center, daily dosing of corticosteroids as initial therapy was equivalent to alternate-day dosing as measured by number and timing of remissions, time to relapse, and relapse rate.<sup>28</sup>

Several retrospective case series have attempted to ascertain patient characteristics that are predictive of response to corticosteroid therapy. In a US study<sup>21</sup> of 40 patients with idiopathic MCD, patients aged <40 years were more likely to be in remission after 8 weeks of therapy with prednisone. Although younger patients may be more likely to achieve rapid remission, their remission is often of shorter duration; 2 independent Japanese studies<sup>22,27</sup> demonstrated that younger patients relapsed earlier and more frequently than older patients. An additional study from Hong Kong<sup>24</sup> also demonstrated that younger patients with MCD (<50 years) were more likely to relapse.

Although definitive data are lacking to guide the optimal dose and duration of initial corticosteroid therapy in adult MCD, one reasonable approach is to give prednisone at 1 mg/kg daily (maximum dose 60-80 mg) for 8 weeks.<sup>33</sup> If remission is achieved, prednisone is then tapered over the subsequent 8 weeks. If remission is not achieved, prednisone is continued for an additional 8 weeks. If remission is still not achieved after 16 weeks of high-dose prednisone, the patient is considered to be steroid-resistant and additional agents are considered (see below). Given the favorable response rate to prednisone and the substantial toxicity of alternative agents, corticosteroids are given as monotherapy initially; co-initiation of cyclophosphamide or cyclosporine is not recommended.

### Adjunctive therapies

The potential complications of NS should be addressed concurrently with treatment for MCD. Loop diuretics are effective for management of symptomatic edema. Hypertension may be treated with any antihypertensive agent including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. Statin therapy should be considered for any patient who remains nephrotic for more than 8 weeks. Warfarin should be initiated for venous thrombosis and continued for 6-12 months regardless of whether symptoms are present. Calcium and vitamin D therapy should be considered for any patient on prolonged steroids to decrease the risk of osteoporosis. Trimethoprim-sulfamethoxazole for prophylaxis against *Pneumocystis carinii* infection should be considered in any patient treated with >15 mg/day of prednisone; dapsone and atovaquone are alternative agents that may be used in patients who are allergic to sulfa-containing antibiotics.

### Subsequent therapy

Although most patients eventually achieve complete remission after an initial course, most case series have indicated that  $\geq 50\%$  of adult MCD patients eventually relapse.<sup>21,27</sup> Relapse is typically treated by re-initiation of prednisone at a dose and duration identical to initial therapy; however, for steroid-resistant patients, additional therapies are necessary to induce remission. Alternative agents are also useful for patients who are steroid-dependent, have frequent relapse, or where steroid side effects are limiting due to brittle diabetes or chronic wounds. These therapies often allow steroids to be tapered or discontinued and thereby mitigate the myriad toxicities caused by corticosteroids (eg, obesity, infection, glucose intolerance, osteoporosis, hypertension, myopathy, and insomnia).

### Cyclophosphamide

The alkylating agent cyclophosphamide has a long history as a therapy for MCD. In 1979, Al-Khader et al<sup>24</sup> reported a controlled trial enrolling 14 patients (ages ranged between 13 and 68; 11 patients aged >20 years) with cyclophosphamide as initial monotherapy for MCD. Eight patients were initially treated with diuretics alone, but only 2 patients in this control group achieved spontaneous remission; 6 additional patients plus 2 patients who were originally in the diuretics-alone control group were treated with cyclophosphamide at 8 mg/kg daily for 2 days followed by 6 mg/kg daily until proteinuria resolved. In the treatment group, 7 of the 8 patients achieved remission within 5 months and no relapses were reported during a mean follow-up of 6 years.

Recent case series have demonstrated the safety and apparent efficacy of cyclophosphamide for steroid-resistant, steroid-dependent, and frequently-relapsing patients. In a retrospective review of 89 adult MCD patients at a single British center, cyclophosphamide was used for steroid-resistant and/or frequently-relapsing patients.<sup>33</sup> Cyclophosphamide was given at a dose of 3 mg/kg/day for 8 weeks; in 36 patients who received the drug, >60% remained in remission at 5 years. Similarly, in a retrospective series from another British center,<sup>23</sup> 63% of 22 patients who had a frequently relapsing course

and received cyclophosphamide at 2-2.5 mg/kg/day for 8 weeks experienced sustained remission for 5 years.

The optimal dose and duration of cyclophosphamide therapy for MCD is unclear. A frequently used regimen consists of cyclophosphamide orally at 2 mg/kg/day for 8-12 weeks. Low-dose prednisone is commonly given concurrently, although there is no evidence to support its efficacy in this setting. For patients with multiple relapses, high-dose prednisone can be used to induce remission prior to initiation of cyclophosphamide. The apparent efficacy of cyclophosphamide for inducing prolonged remission should be balanced against the significant toxicities associated with its use, including infertility, leukopenia, infection, cystitis, and bladder cancer.

### Cyclosporine

Cyclosporine, a calcineurin inhibitor that inhibits T-lymphocyte activation, has been extensively used as a therapeutic option for MCD. As with corticosteroids, most of the high-quality data on its use are derived from studies in pediatric patients. A number of RCTs in children have established the safety and efficacy of cyclosporine as a treatment modality for numerous glomerular disorders, including MCD.<sup>35</sup>

The largest study of cyclosporine therapy in adult MCD patients was performed by the Collaborative Group of the French Society of Nephrology.<sup>36</sup> This trial enrolled 52 patients with steroid-resistant and -dependent MCD. Cyclosporine was given at 5 mg/kg/day concurrently with prednisone. Thirty-six patients (69%) were in remission at 6 months. Unfortunately, recurrences were common when cyclosporine was tapered. Similar results were observed in a smaller Korean trial<sup>37</sup> of 22 adult MCD patients treated with 5 mg/kg/day cyclosporine for 4-8 months. Addition of cyclosporine to steroids was effective in producing complete remission in 80% of patients. However, nearly 60% of patients relapsed over the ensuing 4 months when cyclosporine was tapered or discontinued, demonstrating that patients who responded to cyclosporine often became dependent on the agent.

Cyclosporine has also been studied as a potential monotherapy for inducing remission in MCD. In a Japanese study<sup>38</sup> of 11 adults with either relapsed steroid-sensitive MCD or newly-diagnosed MCD, cyclosporine was given at low doses (1.5-3.1 mg/kg/day); 8 patients (73%) had complete remission within 3 months. Subsequent work by the same group compared low-dose cyclosporine (2-3 mg/kg/day) alone against either cyclosporine with pulse IV methylprednisolone or oral prednisolone alone.<sup>39</sup> Each group was composed of 12 patients with MCD, either newly diagnosed or relapsed; low-dose cyclosporine alone induced complete remission in 75% of patients within 4 months compared with 100% and 92% in the other 2 groups. These results indicate that, although cyclosporine is inferior to corticosteroids as initial therapy for MCD, cyclosporine is safe and effective and could be considered in patients who cannot tolerate steroids.

An international workshop recently convened to develop recommendations for the use of cyclosporine in children and adults with nephrotic syndrome.<sup>35</sup> For patients with MCD, cyclosporine was recommended for adults dependent on or resistant to steroids, or for

those who could not tolerate steroids. Cyclosporine “should be commenced at a dose of 2 mg/kg/day and gradually increased at 2-week intervals until remission is achieved, or the dose is 5 mg/kg/day, or toxicity occurs.”<sup>35</sup> Therapy should be continued for 1-2 years after complete remission is achieved and then slowly tapered. Long-term renal toxicity is a concern with cyclosporine, but it appears that the risk is lower in MCD than for renal transplant recipients. In a follow-up report from the Collaborative French Society of Nephrology study,<sup>40</sup> repeat renal biopsies demonstrated that interstitial and vascular lesions associated with chronic calcineurin-inhibitor exposure were not seen in MCD patients treated with <5.5 mg/kg/day of cyclosporine. Nevertheless, consideration for repeat renal biopsy is recommended for MCD patients on long-term cyclosporine, especially if serum creatinine is rising or the daily dose exceeds 3.5 mg/kg/day.<sup>35</sup> Other toxicities associated with cyclosporine include hypertension, tremor, hypertriglyceridemia, and hirsutism, but these side effects do not usually lead to discontinuation of therapy. It is wise to monitor serum trough levels in all patients on cyclosporine therapy, but the optimal target drug level for MCD therapy has not been established.

#### *Tacrolimus*

Tacrolimus, a recently introduced calcineurin-inhibitor, has been increasingly used as a therapy for steroid-dependent MCD. A small British study<sup>41</sup> followed 10 pediatric patients with NS (9 had MCD, 1 had FSGS), longitudinally; all 10 patients were initially responsive to steroids. Relapses were treated sequentially with courses of numerous therapies including cyclosporine and tacrolimus; no difference in efficacy was noted between the 2 calcineurin inhibitors. Tacrolimus was shown to be effective in inducing remission of steroid-resistant NS in a recent Indian study of 22 pediatric patients.<sup>42</sup> Case reports have also described the successful use of tacrolimus for adult patients with steroid-resistant MCD,<sup>43-45</sup> and a German study<sup>46</sup> reported that 5 of 6 adult patients with steroid-resistant or -dependent MCD responded to tacrolimus therapy (goal trough level was 5-10 ng/mL). Although the data are too limited for conclusions regarding tacrolimus in adult MCD, it is reasonable to consider tacrolimus for patients who are intolerant of cyclosporine due to hypertrichosis or gingival hyperplasia, neither of which is seen with tacrolimus therapy.

#### *Mycophenolate mofetil*

Mycophenolate mofetil (MMF) is another therapy increasingly used in steroid-resistant and -dependent MCD; data from uncontrolled pediatric studies are promising.<sup>47</sup> In adults, a recent literature review<sup>47</sup> of MMF use in glomerular disease identified only 20 adult patients with steroid-resistant and -dependent MCD, collected from several small studies, who had been treated with MMF. Of these patients, 19 had complete or partial remission, allowing steroids to be withdrawn or reduced.<sup>48,49</sup> MMF is typically dosed at 0.5–1 g twice daily; it is generally well-tolerated, although side effects include leukopenia, diarrhea, and gastrointestinal discomfort. MMF should not be used in pregnancy due to the risk of birth defects.

#### *Rituximab*

Rituximab is a humanized monoclonal antibody that targets the B-cell antigen CD20 and leads to depletion of B lymphocytes from the circulation for several months. Three recent case reports describe the use of rituximab in MCD. A 23-year-old woman with a frequently relapsing course of MCD, who had failed therapy with cyclosporine and MMF, experienced a prolonged remission (>28 months) after 4 weekly doses of 375 mg/m<sup>2</sup> of rituximab.<sup>50</sup> Likewise, a 15-year-old girl with MCD, who was dependent on high-dose steroids, underwent a remission after a course of rituximab, allowing for a significant reduction in steroid dose.<sup>51</sup> Finally, rituximab induced a partial remission in a 20-year-old woman, who previously had been nephrotic despite prednisone, tacrolimus, and MMF.<sup>52</sup> These case reports are provocative, not only because of the dramatic results observed in patients who had been highly resistant to therapy, but also because the efficacy of rituximab was unexpected. Whereas MCD is thought to be a disorder of T lymphocytes, rituximab targets B lymphocytes, thus suggesting an interplay between B and T lymphocytes in MCD pathogenesis. Further studies are needed to determine the role of rituximab in the treatment of MCD, and will need to be considered in the context of the risk of viral reactivation (including the Food and Drug Administration alert regarding fatal progressive multifocal leukoencephalopathy in association with rituximab) and the high cost of the drug.

#### **Conclusion**

MCD is an important cause of nephrotic syndrome in children and adults. Corticosteroids are effective as initial therapy in most patients. Rigorous evidence regarding subsequent therapy for steroid-resistant and -dependent disease is scant, making it difficult to make firm recommendations for therapy in such patients. There have been few trials comparing the relative efficacies of steroid-sparing agents, and studies that have been performed in adult MCD patients are small and inconclusive.<sup>28,53</sup> Newer drugs such as MMF and rituximab have shown promise, but further data are needed. Additional work on MCD pathogenesis will hopefully inform future therapeutic trials. Ultimately, to move the field forward, large cooperative trials will be required to examine these therapies in a randomized and controlled fashion. Given the relative infrequency of steroid-resistant MCD, it would be unrealistic to expect enrollment of thousands of patients; however, if multiple centers participated, it would be reasonable to aim for an enrollment that numbered in the hundreds of patients. The National Institutes of Health-supported Focal Segmental Glomerulosclerosis Clinical Trial in Children and Young Adults (FSGS-CT), described in the April 2007 issue of *Nephrology Rounds*, could serve as a model study structure for future cooperative trials on MCD and other glomerular disorders.

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**Dr. Becker** is a fellow in the Renal Division of Brigham and Women's Hospital, Boston, Massachusetts.

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