

The Treatment of Minimal Change Disease in Adults

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ABSTRACT

Minimal change disease (MCD) is the etiology of 10%–25% of cases of nephrotic syndrome in adults. The mainstay of treatment for adult MCD, oral glucocorticoids, is based on two randomized controlled trials and extensive observational data in adults, and this treatment leads to remission in over 80% of cases. Relapses are common, and some patients become steroid-resistant (SR), steroid-dependent (SD), or frequently relapsing (FR). The data guiding the treatment of these patients are limited. Here, we review MCD in adults with particular focus on the evidence for immunosuppressive therapy in these patients.

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Minimal change disease (MCD) is characterized clinically by the nephrotic syndrome (NS) and a renal biopsy that shows no glomerular lesions on light microscopy (or only minimal mesangial prominence), negative staining on immunofluorescence microscopy (or low-level staining for C3 and IgM), and foot process effacement but no electron-dense deposits on electron microscopy.¹ MCD may also be suspected clinically in the absence of a biopsy by exhibiting responsiveness to corticosteroid treatment, and it is sometimes called steroid-sensitive NS. In children, because MCD is the cause of 90% of cases of idiopathic NS and usually exquisitely responsive to steroids, corticosteroid treatment is often initiated without a biopsy, unless clinical and laboratory evidence points to an alternative diagnosis. The causes of NS in adults are more varied, and although some physicians may choose a trial of corticosteroids without histologic evidence of MCD, a kidney biopsy is usually warranted to establish the etiology.

PATHOPHYSIOLOGY

The pathophysiology of MCD is not well understood. The animal model that

most closely resembles MCD is puromycin aminonucleoside nephrosis (PAN) in rats, which leads to the production of reaction oxygen species and direct DNA damage. Histologically, PAN results in alteration of the podocyte actin cytoskeleton, foot process effacement, and detachment from the glomerular basement membrane. Clinically, these changes result in proteinuria.²

In the 1970s, Shalhoub³ proposed that the cause of lipoid nephrosis (a pseudonym for MCD) is a T cell-secreted circulating factor that damages the glomerular basement membrane. Although this circulating factor has not been identified, recent studies highlight a role of immune dysregulation in MCD. T-regulatory (T_{reg}) cells, which attenuate immune responses by suppression of T-effector cells, are dysfunctional in humans with MCD,^{4,5} and augmentation or supplementation of T_{reg} cell function has led to decreased proteinuria in a rat model of the idiopathic NS.⁶

In addition to T_{reg} cell dysfunction, the roles of two podocyte proteins have been explored in MCD: CD80 and angiotensin-like protein 4 (Angptl4).

CD80 (also known as B7–1) is a transmembrane protein that is present on antigen-presenting cells and acts as a costimulatory signal for T cell activation. CD80 is also present in the podocytes of mice in MCD models and is necessary for resulting proteinuria.^{7–9} Soluble urinary CD80 levels are elevated in children and adolescents with MCD in relapse compared with those individuals in remission, patients with other glomerular disease, and control subjects.¹⁰ Furthermore, urinary CD80/creatinine ratios are increased in MCD in relapse compared with MCD in remission or FSGS.¹⁰ Thus, although only explored so far in research settings, CD80 may be a useful biomarker in MCD.

Angptl4 is a secreted glycoprotein that is upregulated in the glomeruli of several models of podocyte injury in rats, including PAN.¹¹ This upregulation is specific to models of steroid-sensitive NS compared with models of membranous nephropathy (passive Heyman nephritis), mesangial injury (Thy1.1 nephritis), and collapsing FSGS (injection of rats with serum from patients with collapsing FSGS). Moreover, a transgenic mouse model showed that upregulation of podocyte Angptl4 results in proteinuria and histologic changes similar to

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those changes seen in MCD. To date, no Angptl4 studies have been conducted in humans with MCD.

Most recently, the upregulation of NF-related κ B has been shown in the nuclei of T and B cells of patients with MCD in relapse compared with patients with MCD in remission, control patients, and patients with membranous nephropathy.¹² This finding implies that NF-related κ B is involved in chromatin remodeling, which enhances transcription factor binding in relapsing MCD.

CLINICAL PRESENTATION

Adults with MCD present with NS: edema, nephrotic-range proteinuria, hypoalbuminemia, and hyperlipidemia. MCD is the etiology of NS in 10%–25% of adults.^{13–15} On urinalysis, microscopic hematuria is present in 10%–30% of adults with MCD^{16–19} and may resolve with disease remission. Most cases are idiopathic, but secondary etiologies must be considered in adults. These latter conditions include malignancies (Hodgkin's lymphoma and thymoma), drugs (nonsteroidal anti-inflammatory drugs and lithium), infections (strongyloides), atopy, and other superimposed renal disease.²⁰

Although MCD in children usually remits within a few weeks of starting corticosteroids, adult MCD responds less rapidly, taking up to 3–4 months of steroid therapy to induce remission. Additionally, 10%–30% of adults may fail to respond to steroid therapy, with a significant proportion of nonresponders showing interstitial fibrosis on the initial biopsy and lesions of FSGS on subsequent biopsies.¹⁸

Adults with MCD present with AKI in 20%–25% of cases.^{18,19} The work by Waldman *et al.*¹⁸ retrospectively examined 95 adults with MCD, 24 (25.2%) of whom met criteria for AKI during either initial presentation ($n=17$) or relapse ($n=7$). Factors associated with AKI were older age, male sex, presence of hypertension, lower serum albumin, and amount of proteinuria. Renal biopsies were performed on 22 patients

during an AKI episode and showed heterogeneous findings: arteriosclerosis (68%), acute tubular injury (64%), interstitial inflammation (59%), mild tubular atrophy with interstitial fibrosis (59%), and interstitial edema (41%). Six patients did not have any of the above injury patterns on renal biopsy. In this series, AKI was associated with higher serum creatinine at last follow-up visit. The correlation of AKI with older age, hypertension, more severe hypoalbuminemia and proteinuria, and arteriosclerosis on renal biopsy had been noted in a prior case control series.²¹

CKD or end stage kidney disease is not typically seen in adult MCD on presentation, and it should prompt the search for other diseases. MCD patients will typically experience relapses, and up to one third of patients may frequently relapse (FR) or become corticosteroid-dependent (SD).^{17,18,22,23} Relapses are also seen in 40% of adults who had MCD during childhood.²⁴

As discussed below, the few controlled studies that have been performed in MCD patients show similar long-term remission rates between treated and nontreated patients.^{25,26} Given the risk of adverse events caused by current treatment modalities, one may ask whether MCD patients should be treated or not. However, the significant comorbidities associated with NS (hyperlipidemia,²⁷ infections,^{16,28} skin breakdown from edema, risk of thromboembolic events,^{29,30} AKI, and worsened quality of life) prompt most physicians to recommend treatment for MCD patients. Importantly, drug-related adverse events become more common in FR and SD patients because of prolonged and repeated exposure to corticosteroids.

TREATMENT OF INITIAL EPISODE OF MCD WITH CORTICOSTEROIDS

Efficacy

Corticosteroid therapy leads to complete remission in over 80% of adults with MCD. The time to complete remission is longer than the time observed in children, with 50% of patients responding by

4 weeks and 10%–25% of patients requiring 12–16 weeks of therapy. Moreover, although alternate-day (every other day) therapy may have a more favorable effect on growth rates in children, the advantages of this regimen in adults have not been proven.^{18,19}

Controlled Trials of Corticosteroid Use in Adults with MCD

There are two randomized trials that have explored the use of corticosteroids in adults with MCD. In 1970, Black *et al.*²⁵ published a multicenter controlled study comparing prednisone (at least 20 mg/d for at least 6 months) with no steroid treatment in 125 adults with NS, 31 of whom had MCD. The steroid group showed a rapid decrease in proteinuria and improvement in edema within the first month of treatment compared with control. Importantly, by 2 years, a significant number of patients in the control group had experienced a spontaneous remission, leading ultimately to similar outcomes with respect to proteinuria, serum albumin, and edema in the two groups (Figure 1).

Similar results were shown in the only placebo-controlled trial of steroid treatment in adult MCD. The work by Coggins²⁶ compared alternate-day prednisone (average dose=125 mg/d) for 2 months with placebo in 28 adult MCD patients. As observed in the work by Black *et al.*,²⁵ steroid-treated patients remitted more rapidly, with 12 of 14 treated patients in complete remission before 2 months compared with 6 of 14 controls. However, there was no difference in overall remission rates over 77 months of follow-up. Adverse events were observed in four patients who were treated with more than one course of steroids.

Beyond these trials, most experience with the use of corticosteroids for adults with MCD is extrapolated from large prospective randomized controlled trials in children^{31,32} and observational studies in children and adults.^{18,19,22,23}

Intravenous Versus Oral Steroid Therapy

The effects of initial therapy with intravenous methylprednisolone compared

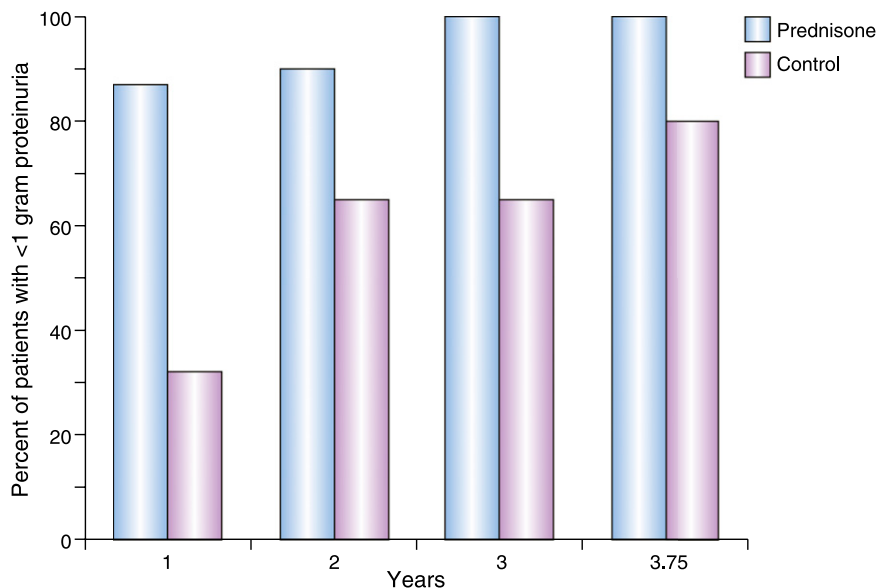


Figure 1. Percentage of MCD patients with more than 1 g of proteinuria treated with prednisone versus no steroid treatment (control). Patients in the steroid group were treated with at least 20 mg/d for at least 6 months. Modified from reference 25, with permission.

with oral prednisone in adult MCD have been studied in two randomized trials. The work by Yeung *et al.*³³ compared the efficacy of intravenous methylprednisolone (20 mg/kg per day for 3 days followed by a 2-week steroid-free period and oral prednisolone at 0.5 mg/kg) with oral prednisolone (1 mg/kg per day for 4–6 weeks followed by a taper) in 18 adults with MCD.³³ At 2 weeks, 3 of 10 (33%) patients treated with intravenous methylprednisolone had attained remission compared with 5 of 7 (71%) of patients with oral prednisolone. The nonresponders in the methylprednisolone group then received oral prednisolone (1 mg/kg per day), and five of seven patients achieved remission. At 1 month, all patients in the prednisolone group had achieved remission. However, this study was limited by small enrollment, and it did not include measurements of proteinuria, renal function, serum albumin, or BP. Moreover, methylprednisolone therapy was considered to have failed if remission was not achieved 2 weeks after therapy, with no oral steroid use during this time.

Imbasciati *et al.*³⁴ performed a multicenter, randomized, prospective trial in 89 patients with MCD, 22 of whom were adults. The study group received

intravenous methylprednisolone for 3 days (20 mg/kg per day) followed by low-dose prednisone for 6 months (starting dose of 0.5 mg/kg per day in adults for 4 weeks followed by taper over 5 months). The control group received high-dose prednisone (1 mg/kg per day in adults) for 4 weeks followed by low-dose prednisone for 5 months. In the adult cohort, remission (decrease of proteinuria to <100 mg/d) occurred in 8 of 11 (73%) study patients compared with 11 of 11 (100%) control patients. No differences were observed in time to response to treatment, number of relapses, or relapse-free event rate at 1 year of follow-up in the adult cohort. More patients in the control group experienced adverse events (obesity and Cushingoid facies) compared with the study group, but a subgroup analysis on adverse events in adults versus children was not performed.

Similar to the study by Yeung *et al.*³³, the trial by Imbasciati *et al.*³³ was limited by small enrollment and did not report important clinical and laboratory data. However, given the higher remission rates observed in the oral prednisone groups combined with the ease of administration of an oral versus intravenous medication, oral steroid therapy is recommended.

Daily Versus Alternate-Day Steroid Therapy

Alternate-day corticosteroid regimens for NS were first described in the 1950s,³⁵ and they have been associated with less adrenal suppression, less effect on growth, and similar efficacy in children. However, no randomized or prospective trials comparing daily with alternate-day dosing have been performed in adults. Observational studies have shown similar remission rates.^{18,36} In the largest series examining daily versus alternate-day steroid regimens, Waldman *et al.*¹⁸ conducted a retrospective analysis of 95 MCD patients over 17 years of age treated at a single center in the United States; 88 of 95 patients were treated with prednisone for an average of 26.6 weeks. The initial dosing regimens were 1 mg/kg per day in 65 patients and 2 mg/kg every other day in 23 patients followed by a taper. There was no significant difference in rate of complete remission between the groups, time to remission, rate of relapse time to first relapse, or adverse events between treatment groups (Figure 2).

Duration and Taper of Steroid Therapy

The optimal duration of corticosteroid therapy is unknown in adults. In children, 6 months of corticosteroid treatment were associated with lower relapse rates compared with 3 months of therapy.³¹ In the retrospective case series by Waldman *et al.*,¹⁸ the majority (>80%) of patients had attained remission by 16 weeks. Given this time to response and the increased risk of adverse events with prolonged courses of high-dose steroid treatment, it is currently recommended that a trial of steroids for 16 weeks be used before declaring a patient a failure of steroid treatment (Table 1).³⁷

The optimal corticosteroid taper protocol in adults is also not known. In children, data support that slow steroid tapers may lead to less steroid dependence and relapse compared with rapid tapers. The work by Ueda *et al.*³⁸ studied 46 incident children diagnosed with steroid-sensitive NS after treatment with high-dose steroids (60 mg/m²) for

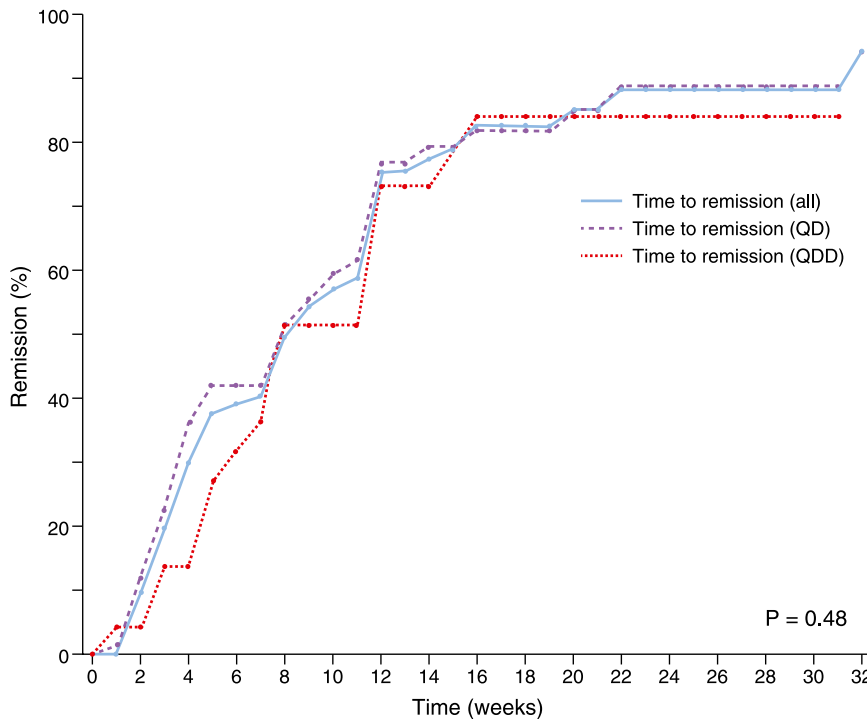


Figure 2. Time to first remission in MCD adults treated with daily versus alternate-day steroids. QD, daily; QOD, every other day. Modified from reference 18, with permission.

4 weeks. They were then randomized to either rapid taper (prednisolone=40 mg/m² for 3 consecutive days per week for 4 weeks) or slow taper (prednisolone=40 mg/m² every other day for 4 weeks followed by a slow taper over 5 months). There was a higher incidence of FR and/or SD in the rapid-

versus slow-taper group at both 6 months (51.7% versus 17.6%) and last follow-up (mean follow-up=46 months, 34.5% versus 5.9%). The slow-taper group initially received a 35% higher steroid dose than the rapid-taper group, but the total cumulative steroid dose at last follow-up was similar between

groups. These data suggest that higher dose and longer taper of steroids lead to improved outcomes in children with MCD.

In adults, no studies comparing rapid versus slow steroid taper exist. Based on case series reports, steroids are usually tapered by 5–10 mg/wk after remission has been achieved for a total period of corticosteroid exposure of at least 24 weeks.^{16, 18,19}

ALTERNATIVE REGIMENS FOR THE INITIAL EPISODE

The data for the use of steroid-sparing regimens in the treatment of the initial MCD episode are limited to case reports and case series. These treatments are reserved for patients who have relative contraindications (severe hyperglycemia or steroid-induced psychosis) or are unwilling to take steroids. Cyclophosphamide^{23,39–42} and cyclosporine⁴³ have been used with response rates of approximately 75% with this limited experience (Table 1).

CORTICOSTEROID-RESISTANT MCD

Steroid-resistant (SR) MCD is defined as failing 16 weeks of corticosteroid

Table 1. Available treatment regimens and published response rates for the initial episode and infrequent relapse of adult MCD

Medication	Regimen	Remission Rates (Complete + Partial)
Initial episode without contraindication to steroids		
Prednisone	Dose: 1 mg/kg per day (maximum 80 mg/day) or 2 mg/kg every other day (maximum 120 mg every other day), for a minimum of 4 weeks, and a maximum of 16 wks (as tolerated). After remission, taper over a total period of corticosteroid exposure of at least 24 weeks.	80%–90%
Initial episode with contraindication to steroids		
Oral CYC	2–2.5 mg/kg per d×8 wk	75%
Cyclosporine	3–5 mg/kg per d in divided doses×1–2 yr	75%
Tacrolimus	0.05–0.1 mg/kg per d in divided doses×1–2 yr	Unknown
Infrequent relapse		
Same as initial medication	Same as initial regimen	Unknown—thought to be similar to initial remission rate

treatment as outlined above. Approximately 10%–20% of adults with MCD are resistant, and a repeat renal biopsy in these patients may show FSGS. This result is associated with a worse prognosis, and treatment regimens should follow the recommendations for steroid-resistant FSGS.³⁷ Available treatment regimens for SR MCD are further described below.

RELAPSE OF MCD

Relapse rates in adult MCD are high, with case series data showing that 56%–76% of patients experience at least one relapse after steroid-induced remission.^{17,18,22,23,44} Relapses are also seen in 40% of adults who had MCD during childhood.²⁴ A course of corticosteroids is usually administered for the first relapse, although there are no trials to support this practice.

Eguchi *et al.*⁴⁵ randomized 52 MCD adults with their first relapse to cyclosporine (area under the curve=1700–2000 ng/ml) plus prednisolone (0.8 mg/kg per day) or prednisolone monotherapy (1 mg/kg per day). Remission was achieved sooner in the cyclosporine group, with the possible additional benefit of lower exposure to steroids. It should be noted that these patients had quiescent courses after their first episode of MCD, with a time from remission to relapse of greater than 2 years.

After an initial relapse episode, MCD patients are classified as infrequent relapsing, FR, SD, or SR (Table 2). These categories are somewhat arbitrary, and the definitions used here are the definitions recently published in the Kidney Disease Improving Global Outcomes Clinical Practice Guideline for Glomerulonephritis.³⁷ Infrequent-relapsing

patients may be treated with a course of corticosteroids identical to their previous regimen when relapse occurs. FR patients are those patients who have had two or more relapses within 6 months of initial response or four or more relapses in any 12-month period. SD patients are those patients who have had two relapses during or within 2 weeks of completing a course of corticosteroids. Up to 33% of patients will become FR (11%–29%) or SD (14%–30%) patients.^{17,18,22,23} FR and SD patients tend to be younger than infrequent relapsers or non-SD patients, and these patients require alternate treatment regimens for future relapses and long-term maintenance therapy. With a repeated course of steroids, some patients may also become SR.

TREATMENT OF FR, SD, AND STEROID-RESISTANT MCD

Alkylating Agents

In retrospective reports (Table 3), oral cyclophosphamide (CYC) leads to remission in a significant number of FR or SD adults with MCD.^{18,19,23,41} The relapse-free interval seems to be longer than with cyclosporine (see below).

The work by Nolasco *et al.*²³ described the use of oral CYC in 36 patients with MCD: CYC was used by 2 patients as primary therapy, 11 patients were SR, 10 patients were SD, and 11 patients were FR. The remission rates were 58% and 69% at 8 and 16 weeks, respectively. The rate of sustained remission in this group was 66% at 4 years. Moreover, the total relapse rate was 40% in the CYC group compared with 76% in the steroid group. The addition of prednisone to CYC did not add benefit in these

patients, and shorter time to remission with initial steroid treatment was associated with shorter time to remission with CYC.

Mak *et al.*¹⁹ used oral CYC at 2–2.5 mg/kg per day for 8 weeks in 22 MCD patients who were SR ($n=2$), were SD ($n=9$), were FR ($n=5$), had steroid psychosis ($n=1$), or were having a first relapse after corticosteroid treatment ($n=5$). The cumulative remission rates in this group were 86%, 74%, and 63% at 1, 3, and 5 years of follow-up compared with 50%, 35%, and 26% for corticosteroid therapy. Within this group, the five FR patients had a high rate of sustained remission (80% at 9.1 years mean follow-up) compared with the SD group, of whom four (44%) patients experienced sustained remission and five (56%) patients experienced additional relapses.

In a retrospective case series, Waldman *et al.*¹⁸ reported the use of oral CYC (mean oral dose=123.6 mg/d, mean duration of therapy=11.5 weeks) in 20 patients. The cumulative remission rate in this cohort was 55% ($n=11$), with a mean time to remission of 6.4 weeks. Remission occurred in 80% of SD ($n=5$) compared with 50% of SR ($n=4$) patients. Seven patients experienced subsequent relapses.

There are two open-label, randomized prospective trials that describe the efficacy of intravenous CYC compared with oral tacrolimus in adults with MCD.^{46,47} Intravenous CYC was chosen because of the higher rates of remission, lower incidence of adverse events, and lower cumulative medication dose of intravenous CYC compared with oral CYC in children with SR-MCD.^{48,49} The first study randomized 26 adults with SD MCD to receive tacrolimus ($n=12$; dosed

Table 2. Definitions of steroid-resistant, steroid dependent, and frequently relapsing MCD

	Definition
Steroid resistant ^a	Failed to achieve remission with 16 wk of daily or alternate-day steroids
Steroid dependent ^a	Two or more relapses during steroid taper or within 2 wk of discontinuing steroid therapy
Frequently relapsing ^b	Two or more relapses within 6 mo or four or more relapses within 1 yr of achieving remission

^aAdapted from adult FSGS guidelines in reference 37.

^bNo formal definition exists in adults; adapted from the definition for children with FR MCD from reference 37.

Table 3. Published experience for the treatment of steroid-resistant, SD, and FR MCD in adults

Medication	Evidence	Regimen	Remission Rates			Relapse Rates		
			SR ^a	SD	FR	SR ^a	SD	FR
Oral CYC	Observational series; one RCT in adults	2–2.5 mg/kg per d×8 wk	50%–80%	50%–80%	50%–80%	50%	25%–56%	25%–56%
iv CYC	Two small RCTs in adults	750 mg/m ² per mo×6 mo + steroids	50%	77%	NA	14%	40%	NA
Cyclosporine ± prednisone	Large observational series data; one small RCT in children and one RCT in adults	3–5 mg/kg per d in divided dose×1–2 yr	45%–92%	45%–92%	45%–92%	NA	62%–75%	62%–75%
Tacrolimus ± prednisone	Small observational series; two small RCTs in adults	0.05–0.1 mg/kg per d in divided dose×1–2 yr	79%–100%	91%–100%	NA	40%	50%	NA
Mycophenolate mofetil	Small observational series; one small RCT in children	1–2 g/d in divided dose	25%	80%–100%	58%	NA	20%–50%	20%–50%

In many studies, the outcomes for these groups are combined. NA, data not available; RCT, randomized controlled trial.

^aIn steroid-resistant cases, review of the initial biopsy and a repeat biopsy may be considered to evaluate for FSGS.

to achieve trough level of 4–8 ng/ml) or intravenous CYC ($n=14$; CYC dose=750 mg/m² monthly) for 24 weeks. Both groups received oral prednisone until remission. At 24 weeks of follow-up, complete remission was achieved in 91% of the tacrolimus group compared with 77% of the intravenous CYC group. Similar remission rates at 48 weeks (50% in the tacrolimus group and 60% in the CYC group) and rates of relapse (40% in the CYC group versus 50% in the tacrolimus group) were observed, and the percentage of patients who were able to become steroid-free was also similar.

The second trial⁴⁹ randomized 37 adults with SR MCD to receive steroids plus either tacrolimus ($n=21$; trough level=5–10 ng/ml) or intravenous CYC ($n=16$; administered monthly for 6 months and then every other month for 6 months, total dose=10 g/1.73 m²) for 1 year; 6-month and 2-year cumulative remission rates were again higher in the tacrolimus group (tacrolimus: 78.9% and 62% versus CYC: 50% and 37.5%). Relapses were more common in the tacrolimus group in this trial. In both trials, the CYC treatment group was older than the tacrolimus group, time to remission was shorter in the tacrolimus group, and there were similar rates of adverse events between treatment groups.

Although a small case series in children showed the use of chlorambucil in MCD,⁵⁰ its use in adult MCD is limited to case reports.⁵¹

Calcineurin Inhibitors

The data on the use of cyclosporine in SD and steroid-responsive adults with MCD are heterogeneous, with many patients receiving additional immunosuppressive therapies. Meyrier *et al.*⁵² conducted a prospective, open-label trial on the use of cyclosporine monotherapy and cyclosporine plus steroids (prednisone=12–15 mg/kg per day) in SD/SR NS patients, 52 of whom had MCD. SD MCD patients had a remission rate of 71% on cyclosporine. Meyrier⁵³ also reported registry data of cyclosporine use in 150 adults with SD or SR NS, 82 of whom had MCD.⁵³ Cyclosporine treatment achieved complete remission in 74% and partial remission in 11% of these patients. Remission rates were higher in patients with SD compared with SR disease. Pooled data from open trials similarly showed 60% complete and 10% partial remission rates in 146 adults and children with SR/SD MCD.⁵⁴

Ponticelli *et al.*⁵⁵ randomized 73 patients (11 adults and 62 children) with FR/SD NS (31 patients with MCD and 42 patients with FSGS) to CYC (2.5 mg/kg per day) for 8 weeks or cyclosporine

(5 mg/kg per day) for 9 months followed by a 3-month taper to withdrawal. At 9 months, 64% (18/28) of patients on CYC and 74% (26/35) of patients on cyclosporine maintained remission ($P = NS$). However, at 2 years, 25% of patients assigned to cyclosporine versus 63% of patients assigned to CYC were still in remission.

In the retrospective case series by Waldman *et al.*,¹⁸ cyclosporine (mean dose=220 mg/d, target trough=150–200 ng/ml) was used in 39 patients (including $n=8$ SD patients and $n=20$ steroid-resistant patients) for a mean duration of 49.5 weeks. Remission was achieved in 61% of these patients, with a mean time to remission of 5 weeks (range=2–9 weeks). A trend to higher remission rates was observed in the SD (75%) compared with the SR (45%) group; 41% of patients relapsed after cyclosporine discontinuation.

The optimal dose, trough level, and duration of cyclosporine therapy are unknown and may be guided by the above studies. Meyrier *et al.*⁵⁶ found the cutoff dose for avoiding renal toxicity on long-term follow-up of adults with SD or SR NS to be 5.5 mg/kg per day. Similar to steroid therapy, slower withdrawal of therapy may decrease relapse rates, and abrupt cessation is associated with the possibility of cyclosporine dependency.

Prolonged treatment in 36 adults (10 patients with MCD and 26 patients with FSGS) for a mean of 26 months followed by slow withdrawal led to sustained remissions without steroids in 11 of 14 patients and sustained remissions with low doses of corticosteroids in 3 patients. In 20% of patients who remained cyclosporine-dependent, doses of <3 mg/kg pr day were sufficient to maintain remission. The cumulative rate of remission peaked at 6 months.^{54,56}

Tacrolimus achieved 6-month and 2-year remission rates of 79%–91% and 50%–62% in SD/SR MCD patients as noted above,^{46,47} and it may allow for the discontinuation of steroids. Tacrolimus has also shown efficacy in case reports⁵⁷ and case series,^{18,58,59} with remission rates of 64%–100% in this limited experience. Moreover, as observed with cyclosporine, relapse after tacrolimus discontinuation compared with CYC favors a slow taper off this medication.⁴⁷

Mycophenolate Mofetil

In children with MCD, mycophenolate mofetil has been used as a steroid-sparing agent. In adults, mycophenolate mofetil has shown efficacy in case reports and small case series,^{18,60–68} with remission rates of 60%–80% in this limited experience.

Rituximab

The use of rituximab in adults with FR and immunosuppression-dependent MCD has been reported in case reports and small uncontrolled case series with some success.^{69–79} These studies indicate that response to treatment is associated with peripheral B cell depletion.

Azathioprine

The use of azathioprine in adults with MCD is not well documented. Historically, azathioprine was not used in difficult-to-treat MCD because of studies in children with FR MCD where azathioprine was not effective.^{80,81} One retrospective series described 13 patients with SR MCD, 5 of whom (on biopsy review) had FSGS, who were treated with azathioprine (2–2.5 mg/kg per day) for 4 years. The time to remission in the MCD

patients was variable at 3–18 months, and all patients continued to be in remission 3–15 years after discontinuation of therapy.⁸² Another case series showed that azathioprine (2 mg/kg per day for 2 years) decreased the number of relapses and prednisolone requirements in seven FR/SD patients with a mean age of 13.5 years who had also failed CYC therapy during childhood.⁸³ Other than these case series, few reports exist of the use of azathioprine in adult MCD.⁴¹

Other Immunomodulatory Treatments for FR, SD, or Steroid-Responsive Disease

The use of levamisole, which has been used in children with MCD, has not been reported in adults. Adrenocorticotropic hormone (ACTH) gel use was reported without success in one patient who had previously failed or relapsed after steroid, MMF, and calcineurin inhibitor therapy,⁸⁴ and ACTH led to partial remission in one of two resistant MCD patients in another case series; this patient relapsed 4 weeks after discontinuing ACTH therapy.⁸⁵ A pilot study recently showed that adding the protease inhibitor saquinavir to immunosuppression regimens in adults and children with SR and SD MCD may decrease proteinuria and steroid requirements in these patients.⁸⁶ Plasma exchange therapy has also been highlighted in case reports in difficult-to-treat patients.^{87,88}

OTHER TREATMENT CONSIDERATIONS IN MCD

Treatment of MCD with Concomitant AKI

AKI can occur in patients with MCD and may be severe enough to require dialysis. As discussed above, risk factors for AKI in MCD include older age, hypertension, severe NS, and arteriosclerosis on renal biopsy.^{18,21} Kidney function typically recovers even in the most severely affected patients, although patients who have experienced AKI may have residual chronic renal impairment.¹⁸ Careful attention to patients' volume status, supportive therapy for AKI, and continued

therapy with corticosteroids are suggested. Albumin infusion may be considered if there is evidence of severe intravascular volume depletion with severe hypoalbuminemia.

Nonimmunomodulatory Therapies for MCD

Because proteinuria and hyperlipidemia in MCD typically improve with disease remission, the success of corticosteroid therapy usually obviates the need for inhibitors of the renin-angiotensin-aldosterone system or statin therapy during initial MCD episodes or infrequent relapses. One study of 40 adults who had relapsing NS as children did not show a higher incidence of cardiovascular disease, implying that long-term cardiovascular risk was not increased by intermittent hyperlipidemia during nephrotic relapses in childhood, although this study was small and no firm conclusion can be derived from the data.⁸⁹ The use of renin-angiotensin-aldosterone blockers and statins may be considered on a case-by-case basis in MCD adults, particularly those patients with hypertension.

CONCLUSION

Adults with NS caused by MCD continue to pose a challenge to clinicians. Unless a contraindication exists, corticosteroids (with daily or alternate-day dosing) continue to be first-line therapy for MCD in adults, with longer treatment duration and slower tapers required compared with children to attain remission and minimize relapses. Relapse is common, and many patients will become FR, SD, or SR. The availability of nonsteroidal immunomodulatory therapies allows the treatment of complicated and resistant patients to be tailored individually based on the adverse event profiles of these medications. Preclinical and patient-based research studies continue to shed light on this poorly understood disease.

DISCLOSURES

None.

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