

Chapter 5: Minimal-change disease in adults

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INTRODUCTION

This chapter makes treatment recommendations for adults with MCD. The cost implications for global application of this guideline are addressed in Chapter 2.

5.1: Treatment of initial episode of adult MCD

- 5.1.1: We recommend that corticosteroids be given for initial treatment of nephrotic syndrome. (1C)
- 5.1.2: We suggest prednisone or prednisolone* be given at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg). (2C)
- 5.1.3: We suggest the initial high dose of corticosteroids, if tolerated, be maintained for a minimum period of 4 weeks if complete remission is achieved, and for a maximum period of 16 weeks if complete remission is not achieved. (2C)
- 5.1.4: In patients who remit, we suggest that corticosteroids be tapered slowly over a total period of up to 6 months after achieving remission. (2D)
- 5.1.5: For patients with relative contraindications or intolerance to high-dose corticosteroids (e.g., uncontrolled diabetes, psychiatric conditions, severe osteoporosis), we suggest oral cyclophosphamide or CNIs as discussed in frequently relapsing MCD. (2D)
- 5.1.6: We suggest using the same initial dose and duration of corticosteroids for infrequent relapses as in Recommendations 5.1.2, 5.1.3, and 5.1.4. (2D)

*Prednisone and prednisolone are equivalent, used in the same dosage, and have both been used in RCTs depending on the country of origin. All later references to prednisone in this chapter refer to prednisone or prednisolone. All later references to oral corticosteroids refer to prednisone or prednisolone.

BACKGROUND

MCD refers to the occurrence of nephrotic syndrome with no glomerular lesions by light microscopy (or only minimal mesangial prominence), no staining on immunofluorescence microscopy (or low-intensity staining for C3 and IgM), and foot process effacement but no electron-dense deposits on electron microscopy.¹²¹

Although spontaneous remission can occur in MCD,^{122–125} untreated nephrotic syndrome is associated with significant

morbidity due to accelerated atherosclerosis, in part due to dyslipidemia,¹²⁶ infections,^{125,127} and thromboembolic events.¹²⁸ Therefore, specific treatment should be given with the goal of achieving remission. The cornerstone of treatment has been corticosteroids. MCD in children is exquisitely sensitive to corticosteroids; however, adults tend to respond more slowly, with responses occurring as late as 3–4 months after starting therapy. The response to corticosteroids is also less predictable in adults, as only about 75% of adults with MCD are steroid-responsive (Table 8). Also, in contrast to children, there is a paucity of well-designed RCTs investigating the treatment of MCD in adults.

Although AKI is common in adults with MCD (up to 20–25%),^{129,130} progressive CKD is not part of the natural history of adults with MCD, and its occurrence suggests underlying FSGS.

More than half of adult MCD patients will experience relapses, and up to a third of patients may become frequent relapsers or corticosteroid-dependent.^{130–133} Furthermore, a 40% relapse rate has been reported in adults who had MCD as children,¹⁶ and these patients continue to relapse. Secondary etiologies associated with MCD are uncommon, but should be considered. They include Hodgkin's disease, lithium therapy, and nonsteroidal anti-inflammatory drugs.¹³⁴

Corticosteroids are generally well-tolerated, but drug-related adverse effects are common with prolonged/repeated courses in SD or FR patients.

Disease Definitions

Definitions of proteinuria outcomes are as listed in Table 10, Chapter 6. Partial remissions in proteinuria are not seen in MCD.

RATIONALE

- There is only low-quality evidence to recommend corticosteroids in the treatment of adult MCD. This recommendation is based largely on extrapolation from RCTs in children, as well as small RCTs and observational studies in adults.
- There is only low-quality evidence to define the optimal dose and duration of corticosteroids in adults, but a high dose until remission is achieved followed by a slow taper to minimize relapse is usually prescribed.
- There is very low-quality evidence suggesting that alternate-day is equivalent to daily corticosteroids in adult MCD.
- MCD in adults may take a longer time to remit compared to MCD in children.

Table 8 | Dosage regimens in MCD

Drug and dosing scheme
Initial treatment
Prednisone
Daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg)
–until complete remission (minimum 4 weeks to a maximum of 16 weeks)
–after complete remission, tapered slowly over 6 months
FR or SD MCD
1. Cyclophosphamide (oral) single course 2–2.5 mg/kg/d as tolerated for 8 weeks
2. Relapsed despite cyclophosphamide, or patients of childbearing age
a. Cyclosporine starting dose 3–5 mg/kg/d (in two equally divided doses)
b. Tacrolimus 0.05–0.1 mg/kg/d (in two equally divided doses) Following 3 months of stable remission, tapered to reach the minimum dosage that maintains remission, for 1–2 years
3. Intolerant to corticosteroids, cyclophosphamide, and/or CNIs
a. Mycophenolate mofetil 500–1000 mg twice daily for 1–2 years

FR, frequently relapsing; MCD, minimal-change disease; SD, steroid-dependent.

Corticosteroids have been studied in several large prospective RCTs in children^{99,135} and observational studies in children and adults.^{129–133} In a very early multicenter controlled study of corticosteroids compared to no treatment in 125 nephrotic adults (including 31 MCD patients defined by light microscopy alone), those treated with at least 20 mg/d prednisone for at least 6 months showed an early and rapid decrease in proteinuria compared to the control group. However, by two and a half years, there was no difference in proteinuria or serum albumin in the two groups.¹²³ Similarly, in one small RCT of 28 adult MCD patients that compared prednisone 125 mg every other day for 2 months with placebo, there was no difference in overall remission rates over 77 months follow-up, although a significant percentage of the placebo arm ended up being treated with prednisone over this time frame. However, patients treated with prednisone went into remission more rapidly; 12 of 14 treated patients were in complete remission before 2 months, compared to 6 of 14 controls.^{124,136}

Although there are no controlled trials comparing daily vs. alternate-day corticosteroids in adults, observational studies have not shown any difference in response rates.¹³⁰ Corticosteroid therapy leads to complete remission in over 80% of adults with MCD. The time course to a complete remission is delayed compared to children, with 50% responding by 4 weeks but the remaining 10–25% requiring 12–16 weeks of therapy.^{129,130} It is known that, in children, 6 months of corticosteroid treatment is associated with a lower relapse rate than 3 months of therapy.¹³⁵ The optimal method to taper corticosteroids in adults is not known, but corticosteroids are commonly tapered by 5–10 mg/wk or less after achieving remission, for a total period of corticosteroid exposure of at least 24 weeks.^{125,129,130}

Only a few patients have been treated at the time of initial presentation with steroid-free regimens (e.g., cyclophosphamide^{132,137,138} or cyclosporine¹³⁹). In this very limited experience, the typical response rate of 75% is comparable to corticosteroids.

For infrequent relapses, repeat courses of corticosteroids may be used as in the first episode of MCD. There are no RCTs to guide the therapy of relapse in adult MCD. Reinstitution of prednisone usually results in a remission.

5.2: FR/SD MCD

5.2.1: We suggest oral cyclophosphamide 2–2.5 mg/kg/d for 8 weeks. (2C)

5.2.2: We suggest CNI (cyclosporine 3–5 mg/kg/d or tacrolimus 0.05–0.1 mg/kg/d in divided doses) for 1–2 years for FR/SD MCD patients who have relapsed despite cyclophosphamide, or for people who wish to preserve their fertility. (2C)

5.2.3: We suggest MMF 500–1000 mg twice daily for 1–2 years for patients who are intolerant of corticosteroids, cyclophosphamide, and CNIs. (2D)

RATIONALE

- There is low-quality evidence to suggest the value of alkylating agents in adult FR/SD MCD. Support for this approach comes from RCTs in children, and observational studies in adults.
- There is low-quality evidence to suggest that CNIs can induce complete or partial remission in adult MCD, but relapse rates may be higher than with alkylating agents after cessation of CNIs.
- There is very low-quality evidence to suggest the use of MMF as a corticosteroid or CNI-sparing agent.

In observational studies, treatment with cyclophosphamide leads to remission in a significant number of adults.^{129,130,132} The relapse-free interval appears to be longer than with cyclosporine (see below). In an observational study, the initial response rates with cyclophosphamide in SD adults appeared excellent (all nine patients were able to be weaned off steroids in one study);¹²⁹ however, five of these patients relapsed. In this study FR MCD patients appeared to fare better than SD MCD, with 80% of patients showing sustained remission at a mean follow-up of 9.1 years. Similarly, SD children may be less responsive to cyclophosphamide than frequent relapsers.⁴³ In another study, 21 of 36 adults with FR/SD MCD attained remission within 8 weeks and four more patients (total of 25/31 or 69%) within 16 weeks. The addition of prednisone to cyclophosphamide did not appear to provide added benefit. Remissions appeared to be more durable with cyclophosphamide compared to steroids.¹³² In another study, 55% of 20 patients treated with cyclophosphamide (for FR or SD MCD) had a complete or partial remission.¹³⁰ There is one report of the effectiveness of regimens using i.v. cyclophosphamide in adults.¹⁴⁰

Many observational studies have reported the efficacy of cyclosporine with remission rates of 70-90%.^{130,141} In an RCT of 73 adults and children with FR/SD nephrotic syndrome (31 with MCD; 42 with FSGS), treatment was given with either cyclophosphamide (2.5 mg/kg/d) for 8 weeks or cyclosporine (5 mg/kg/d) for 9 months, followed by a 3-month taper to withdrawal. At 9 months, remission rate did not differ significantly: 64% (18/28) of patients on cyclophosphamide and 74% (26/35) of patients on cyclosporine maintained remission. However, at 2 years, 25% of patients assigned to cyclosporine vs. 63% of patients assigned to cyclophosphamide were still in remission.⁶² Another RCT of 52 patients noted that remission was achieved sooner in patients treated with cyclosporine plus 0.8 mg/kg/d prednisone compared to patients receiving only 1 mg/kg/d prednisone, suggesting an additional benefit of lower exposure to corticosteroids (Online Suppl Tables 20, 21).¹⁴²

The optimal dose and duration of cyclosporine therapy is unknown. In an RCT of adults and children with FR/SD nephrotic syndrome, cyclosporine was dosed at 5 mg/kg/d for 9 months followed by a taper over 3 months.⁶² The possibility of cyclosporine dependency is high when treatment is abruptly stopped after achieving complete remission. However, prolonged treatment in 36 adult patients for a mean of 26 months, followed by slow withdrawal, led to sustained remissions without steroids in 11 of 14 patients and with low doses of corticosteroids in three patients. In 20% of patients, who remained cyclosporine-dependent, doses of <3 mg/kg/d were sufficient to maintain remission. The cumulative rate of remissions appears to reach a plateau by 6 months.^{143,144}

Tacrolimus, administered for 24 weeks was compared to i.v. cyclophosphamide in a small RCT in SD patients with achieved response rates similar to cyclosporine. All patients in this study were able to discontinue corticosteroids.¹⁴⁰

There are insufficient data to suggest a therapeutic level for CNI in adult MCD patients. After starting the drug with the suggested dosing regimen in Table 8 and achieving remission, the CNI dose should be progressively reduced to the lowest level that will maintain the remission. Many patients will be able to come off corticosteroids completely¹⁴⁰ and every effort should be made to reduce and stop corticosteroids after starting CNI.

In children with MCD, MMF has been used as a steroid-sparing agent (see Recommendation 3.3.5). The experience with MMF in adults has been limited to case reports.¹⁴⁵⁻¹⁴⁷

5.3: Corticosteroid-resistant MCD

5.3.1: Re-evaluate patients who are corticosteroid-resistant for other causes of nephrotic syndrome. (Not Graded)

RATIONALE

- Corticosteroid-resistant MCD suggests FSGS.

An estimated 10% of adult MCD patients are steroid-resistant (failed 16 weeks of daily or alternate-day corticosteroids as

outlined previously). Steroid resistance may be due to undetected FSGS (which may not be seen in a biopsy specimen because it is a focal lesion). A repeat biopsy could be considered and may show FSGS, which is associated with a worse prognosis than MCD. There are no RCTs and very few observational data on treatment strategies of steroid-resistant MCD in adults. Treatment strategy as outlined in Chapter 6 is suggested.

5.4: Supportive therapy

5.4.1: We suggest that MCD patients who have AKI be treated with renal replacement therapy as indicated, but together with corticosteroids, as for a first episode of MCD. (2D)

5.4.2: We suggest that, for the initial episode of nephrotic syndrome associated with MCD, statins not be used to treat hyperlipidemia, and ACE-I or ARBs not be used in normotensive patients to lower proteinuria. (2D)

RATIONALE

- AKI may accompany MCD in adults. This is usually reversible with continued steroid therapy. Supportive care, including renal replacement therapy, may be temporarily required. Proteinuria in adult MCD will typically remit with corticosteroids. As a consequence, the accompanying hyperlipidemia will remit with resolution of proteinuria, negating the need for statin therapy.
- Proteinuria in adult MCD will typically remit with corticosteroids, and statins and RAS blockade to help reduce proteinuria are not necessary if early remission is achieved.

AKI, sometimes severe enough to require dialysis, can occur in patients with MCD. Risk factors include older age, hypertension, severe nephrotic syndrome, and underlying arteriosclerosis of the kidney.^{130,148} Kidney function typically recovers even in the most severely affected patients, although patients who have experienced kidney failure may have residual chronic renal impairment.¹³⁰ Careful attention to volume status, as well as continued therapy with corticosteroids, and other supportive therapy for AKI are suggested.

There is only one small study of 40 adults who had relapsing nephrotic syndrome as children. This study 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.¹⁴⁹ The use of antihyperlipidemic agents and ACE-I or ARBs may be considered on a case-by-case basis in FR/SD MCD adults in whom rapid remission is not achieved. It is important to note that adding an ACE-I or ARB in a severely nephrotic patient who is being aggressively diuresed may precipitate AKI.¹⁵⁰

Economic Considerations

Prednisone and cyclophosphamide are less costly than CNIs and MMF. Cost factors need to be considered in patients who are not able to afford or access the more expensive medications.¹⁵¹ The addition of ketoconazole is safe and can lead

to significant reduction in costs associated with CNIs, but drug levels need to be assessed to avoid nephrotoxicity.⁷³

RESEARCH RECOMMENDATIONS

- RCTs should investigate the use of CNIs or MMF as alternatives to corticosteroids for the first episode of adult MCD.
- RCTs are needed to compare CNIs to cyclophosphamide in FR/SD MCD, and to establish if cyclosporine or tacrolimus should be the preferred CNI.
- RCTs are needed to study the role of rituximab in FR/SD MCD.
- RCTs are needed to study the role of levamisole in FR/SD MCD.
- Evidence should be collected in these RCTs to evaluate the long-term cardiovascular, metabolic, infectious, and bone risk of FR/SD MCD, and corresponding treatment.

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SUPPLEMENTARY MATERIAL

Supplementary Table 20: Summary table of RCT examining CsA vs. steroid treatment after first relapse in adults with minimal change disease (categorical outcomes).

Supplementary Table 21: Summary table of RCT examining CsA vs. steroid treatment after first relapse in adults with minimal change disease (continuous outcomes).

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php