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Steroid Minimization in Adults with Minimal Change Disease

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Glomerular disease · Minimal change disease · Glucocorticoids · Nephrotic syndrome · Immunosuppression · Tacrolimus · Rituximab · Mycophenolate

Abstract
Background: Minimal change disease (MCD) causes approximately 10% of nephrotic syndrome in adults. While glucocorticoids (GCs) effectively induce remission in MCD, the disease has a high relapse rate (50–75%), and repeated exposure to GCs is often required. The adverse effects of GCs are well recognized and commonly encountered with the high doses and recurrent courses used in MCD. ***Summary:*** In this review, we will discuss the standard therapy of MCD in adults and then describe new therapeutic options in induction therapy and treatment of relapses in MCD, minimizing the exposure to GCs. ***Key Messages:*** Steroid minimization strategies may decrease adverse effects in the treatment of MCD.

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Introduction

Minimal change disease (MCD) is the commonest cause of nephrotic syndrome (NS) in children and accounts for ~10% of NS in adults [1–3]. Corticosteroids have long been the backbone of treatment for many forms of glomerular disease and are usually very effective in MCD. Most adults and children with MCD respond briskly to treatment with high-dose prednisone or prednisolone, but high-dose glucocorticoids (GCs), and in particular, recurrent courses of GC, are associated with a wide range of serious side effects. The adverse consequences of high-dose GC are increasingly recognized, and multiple recent studies in a range of glomerular diseases are now using much lower doses of GC [4–8]. Emerging data in MCD now suggest alternative therapies to GC which may have more favorable side effect profiles.

Proposed Mechanism of Action for GCs in MCD

MCD is primarily a disorder of the podocyte (podocytopathy) as illustrated by the diffuse foot process effacement seen on electron microscopy, however, the underlying pathophysiology remains unclear. In the absence of clearly deposited immunoglobulin or complement in kidney biopsies, prior studies have focused on the role of T cell dysfunction (reviewed by Saleem and Kobayashi [9]). Abnormalities in T-regulatory cells, which attenuate immune responses by suppressing T-effector cells, have been described [10]. Upregulation of CD80, a transmembrane protein present on antigen-presenting cells that acts as a costimulatory signal for T cell activation, has been noted, and increased urinary CD80 levels have been proposed as a biomarker for active MCD [11]. Interleukin-13 produced by Th2 T cells has been shown to cause podocyte injury in an animal model of MCD [12]. By contrast, recent studies have demonstrated beneficial effects of rituximab in the treatment of MCD, suggesting a role

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Table 1. Clinical features of MCD at the time of kidney biopsy in 4 large retrospective case series

	Szeto et al. [27]	Fenton et al. [28]	Waldman et al. [26]	Maas et al. [29]
Series	*n* = 340, China	*n* = 78, UK	*n* = 95, New York	*n* = 125, The Netherlands
Age, years	38	36	45	46
Sex (female), %	44	40	61	58
Microhematuria, %	23	15	29	*
Proteinuria, g/day	4.9	5	9.9	9.6
Serum creatinine, mg/dL	0.9	1.0	1.4	0.9
AKI, %	14	28 in the entire cohort (37 with first MCD presentation)	18	40
Hypertension, %	21	*	43	37

MCD, minimal change disease. * Data not available.

for B cells in MCD [13]. Alterations in immunoglobulin subclasses have been described in NS, and plasma soluble CD23, a classic B cell activation marker, is increased in the relapse of NS [14]. Nephrin distribution in the podocyte foot processes is altered in MCD [15]. Anti-nephrin antibodies produce an MCD-like lesion in animal models [16], and have been proposed to play a role in human MCD [17].

GC exert anti-inflammatory and immunosuppressive effects by both genomic and nongenomic pathways. GC and their cytoplasmic receptors form a complex that enters the nucleus and binds to specific GC response elements within genes [18]. This increases the expression of anti-inflammatory proteins (transactivation) or decreases the production of pro-inflammatory proteins (transrepression) [18]. Many of the adverse effects of GC are induced by transactivation, whereas the beneficial anti-inflammatory effects are mainly due to transrepression [18]. Much of GC immunosuppressive properties are through nongenomic effects mediated by membrane GC receptors, partly through inhibition of the NF-kB transcription factor pathway in lymphocytes [18, 19].

It has long been assumed that the beneficial effects of GC in MCD are related to these immunosuppressive effects, however, GC may have direct protective effects on podocytes. Experimental studies suggest that corticosteroids may protect podocytes from injury. Cultured podocytes express the key components of the GC receptor complex, including heat shock protein 90 and the immunophilins FKBP51 and FKBP52 [20]. In human cultured podocytes, dexamethasone treatment for 24 h increased the phosphorylation of nephrin and stabilized the podocyte actin cytoskeleton [21]. Prednisone reduced podocyte apoptosis and increased the number of podocyte progenitors in a murine model of FSGS [22]. Dexamethasone pretreated murine podocytes stimulated with Ang II prevented podocyte motility and actin disassembly via modulation of cGMP production [23].

Traditional GC Treatment of MCD in Adults

The traditional therapy of MCD is induction with high-dose GC (prednisone or prednisolone). GC therapy has been well studied in several large prospective randomized trials in children and observational studies in adults (Tables 1 and 2 provide data from the four largest retrospective series in adults).

In the only randomized controlled trial with prednisone in adults with MCD published in 1970, 31 adult patients with MCD were treated with low-dose prednisone (<30 mg daily) versus nonspecific therapy as control [24]. More than 75% of low-dose prednisone-treated patients had remission of proteinuria to <1 g/day within 6 months. By comparison, 50% of those in the untreated group were in remission at 18 months and approximately 70% at 3 years. Of note, 5–10% of the patients spontaneously remitted within 3 months in the untreated group.

A traditional steroid regimen for MCD in adult patients is oral prednisone 1 mg/kg (up to 80 mg/day) or 2 mg/kg on alternate days (up to 120 mg/day) for a minimum of 4 weeks and a maximum of 16 weeks (as tolerated). After remission, GC is tapered over at least 24 weeks.

Efficacy of GCs in the Treatment of MCD

More than 85% of children attain remission after 8 weeks of steroid therapy compared to about 70% of adults (aged 15–39 years), but only 30% of adults aged

Table 2. Response to glucocorticoid therapy in MCD in 4 large retrospective case series

	Szeto et al. [27]	Fenton et al. [28]	Waldman et al. [26]	Maas et al. [29]
Series	*n* = 340, China	*n* = 78, UK	*n* = 95, New York	*n* = 125, The Netherlands
Time to remission (median)	10 weeks	5 weeks (2–11 weeks)	13 weeks	68% (8 weeks) 88% (16 weeks)
Steroid resistant, %	10	10	27	10
Relapse rate, %	38	61	73	54
Median time to relapse	*	11 months	22 weeks	9 months
Frequently relapsing/steroid dependent, %	25	43	29	16
Complications, %	VTE (3) Major infection (5) DM (18)	VTE (12) Infection (14) DM (12)	VTE (4) Infection (7) DM (1)	VTE (9) Infection (12) DM (7)
Median follow-up	175 months (120–235 months)	72 months (6–190 months)	139 weeks (119–420)	59 months (4–308)

MCD, minimal change disease. * Data not available.

Table 3. Adverse effects of corticosteroids [39]

System	Adverse effects
Musculoskeletal	Osteoporosis, avascular necrosis, myopathy
Endocrine and metabolic	Glucose intolerance and diabetes, fat redistribution and obesity, suppression of sex hormone secretion
Cardiovascular	Dyslipidemia, premature atherosclerosis and cardiovascular disease, sodium retention and hypertension, edema
Dermatological	Cutaneous atrophy, acne, hirsutism, alopecia
Ophthalmological	Cataract, glaucoma
Gastrointestinal	Peptic ulcer disease, gastritis, gastrointestinal bleeding, pancreatitis
Infectious	Viral, bacterial, fungal infections
Psychological and behavioral disturbances	Steroid psychosis, mood disturbances

40–78 years achieve remission with 8 weeks of steroid treatment. With more prolonged treatment (up to 24 weeks), 90% of adults with MCD will achieve a complete remission (CR), but at the expense of markedly increased GC exposure [25]. Even though MCD is usually steroid-responsive, relapse of NS following discontinuation of initial steroid therapy is very common. The relapse rate in adults is 50–75% [26–29], and about 30% of adults will develop frequent relapses (≥2 relapses in 6 months or ≥4 relapses in 1 year) or become steroid-dependent (relapse during steroid taper or 15 days after GC discontinuation) [25, 26, 30] (Table 2). Occasional, infrequent relapses in GC responsive patients are usually treated with a short course of prednisone. Continuous low-dose alternate-day prednisone may sustain remission in some steroid-dependent and frequently relapsing MCD, but often results in a high cumulative GC exposure over time.

Adverse Effects of GC Treatment in MCD

Despite the many beneficial effects, long-term GC exposure is associated with multiple adverse effects, including infection, bone disease, dysglycemia, obesity, hypertension, psychosis, gastrointestinal bleeding, cataracts, and long-term risks of cardiovascular disease (Table 3) [27, 31–36]. The response to induction therapy in adults with GC is often delayed compared to children, and longer courses of GC are commonly prescribed [25, 26]. As MCD often follows a relapsing course, patients are exposed to repeated doses of corticosteroids which increases the long-term cumulative GC exposure [37–40].

Infection risk: Although proteinuria is more selective in MCD compared to other glomerular diseases such as FSGS or membranous nephropathy, loss of immunoglobulin and complement proteins in the urine of

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Table 4. Steroid minimization approaches in MCD: induction of remission

Medication	Evidence	Regimen	Remission rate (study drug vs. GC)	Relapse rate (study drug vs. GC)	Time to relapse
Short GC course					
Ozeki et al. [8]	Prospective, observational study of new-onset MCD treated with short GC course (n = 35) vs. traditional (n = 140) GC (1–2 years)	Short GC course: prednisolone 0.8–1.0 mg/kg/day continued for 4–6 weeks; then, dosage reduced to 0.5–0.6 mg/kg alternate days, discontinued after 4 weeks Traditional GC course: prednisolone 1 mg/kg/day with slow taper over 1–2 years	CR: 100% (short course) vs. 100% (traditional) (time to CR 13 vs. 12 days, p = 0.91)	Relapse rate: 68.8% (short course) vs. 53.6% (traditional) (p = 0.1) Frequent relapses: 14.3% (short course) vs. 13.6% (traditional GC) (p = 0.91)	159 days (short course) vs. 357 days (traditional) (p < 0.001)
Mycophenolate sodium and low-dose prednisone					
Rémy et al. [51] (MSN study)	Open-label RCT in 32 French centers with 116 adults with de novo or first relapse of MCD randomized to low-dose prednisone + myfortic (n = 58) vs. high-dose prednisone for 24 weeks (n = 58)	Test group: low-dose prednisone (0.5 mg/kg/day, 40 mg max) plus enteric-coated mycophenolate sodium (720 mg) twice daily for 24 weeks Control group prednisone 1 mg/kg/day for 24 weeks	CR (4 weeks) 64.9 vs. 57.9% (p = NS) CR (8 weeks) 82.6 vs. 70% (p = NS) CR (24 weeks) 80.4 vs. 79.6% (p = NS) CR (52 weeks) 67.5 vs.78.9% (p = NS)	Relapse rates: 18.8% (MPA) vs. 27.3% (Pred) (p = NS)	Median time to relapse 7.1 vs. 5.1 months (p = NS)
TAC monotherapy					
Medjeral-Thomas et al. [50] (minTAC study)	Multicenter RCT in the UK in adults with de novo MCD. Patients randomized to TAC (n = 25) or prednisolone (n = 25) for 4 months	TAC: 0.05 mg/kg twice daily, target trough 6–8 ng/mL for 12 weeks after CR, then dose reduced over 8 weeks and stopped Prednisolone: 1 mg/kg/day up to 60 mg daily; 1 week after achieving CR, the steroid dose was halved for 4–6 weeks and tapered over 6 weeks (16 weeks of GC)	CR (4 weeks) 22 vs. 64% (p = 0.005) CR (8 weeks) 68 vs. 84% CR (16 weeks) 76 vs. 92% CR (26 weeks) 88 vs. 92% (p = NS)	Relapse rate after achieving CR 73 vs. 74% (p = 0.99)	Median time from CR to relapse 33 weeks (TAC) vs. 22 weeks (GC)
TAC monotherapy after pulsed MP					
Li et al. [52]	Prospective, open-label, multicenter, RCT in China. Patients randomized to TAC (n = 63) vs. prednisone (n = 56) following a 10-day course of IV MP	TAC 0.05 mg/kg/day, target trough 4–8 ng/mL, maintained for 16–20 weeks, then tapered to trough 2–5 ng/mL over 18 weeks until withdrawal Prednisone 1 mg/kg/day (max. 80 mg) for 6–8 weeks, tapered over 5–6 months Both groups received an initial 10-day course of IV MP (0.8 mg/kg)	CR 98.3 vs. 96.2% (p = NS) Mean time to remission 2.6 vs. 2.7 weeks (p = NS)	Relapse rates 45.5 vs. 49.0% Frequent relapsers (7.3 vs. 3.7%, p = NS)	Mean time to relapse 23.3±16.9 weeks vs. 24.2±15.4 weeks (p = NS)

Table 4 (continued)

Medication	Evidence	Regimen	Remission rate (study drug vs. GC)	Relapse rate (study drug vs. GC)	Time to relapse
Tacrolimus plus low-dose GC					
Chin et al. [53]	Open-label, multicenter, noninferiority trial in Korean adults with MCD (68 de novo and 68 relapsed). Randomized to TAC plus low-dose prednisolone (n = 69) or standard dose prednisolone (n = 75) for 24 weeks	Tacrolimus and low-dose prednisolone: tacrolimus 0.05 mg/kg twice daily (goal trough 5–10 ng/mL) plus low-dose prednisolone (0.5 mg/kg daily) Standard dose prednisolone:1 mg/kg/day for up to 8 weeks or until achieving CR Two weeks after CR, the GC dose tapered to maintenance 5–7.5 mg/day in both groups, and the TAC dose lowered to maintenance dose (goal trough 3–8 ng/mL)	CR rates 79.1 vs. 76.8% (p = NS)	Relapse rates 5.7% (TAC + LD Pred) vs. 22.6% (GC) (p = 0.01)	Median time to relapse not reached
CsA					
Shirai et al. [54]	Pilot study, open-label RCT in Japanese adults with new-onset MCD randomized to CsA + prednisolone (n = 11) or prednisolone only (n = 10)	Both groups prednisolone (0.8 mg/kg) until 2 weeks after achieving proteinuria ≤1 g/day CsA (2 mg/kg, goal CsA C2 level 600–1,200 ng/mL) + steroid taper by 4 months vs. a prolonged prednisolone taper over 18 months	CR (4 weeks) 91 vs. 100% (p = 0.32) Time to remission:19.9±20.2 vs. 16.6±7.2 days	Relapse rate (18 months) 27.2 vs. 60% (p = NS) Relapse rate (30 months) 64 vs. 70% (p = NS) C2 values significantly higher in relapse-free subjects at 18 months (749.3±156.2 vs. 535.3±176.9 ng/mL; p = 0.048)	Data not available
Matsumoto et al. [55]	Prospective observational study in Japan of 26 de novo and 10 relapsed adult MCD patients CsA alone (n = 12) vs. CsA and intravenous methylprednisolone (n = 12) vs. prednisolone only (n = 12)	CsA dose 2–3 mg/kg/day (trough ≤150 ng/mL), continued for 12 months, then tapered by 25 mg every 2 months.±IVMP 1,000 mg daily for 3 days. Prednisolone alone: (40–60 mg/day) for 4–6 weeks, with slow taper	CR: 75% (CsA) vs. 100% (CsA/IVMP) vs. 92% (Pred) (p = 0.04) Median time to remission: 40.9±35.5 days (CsA) vs. 11.0±5.6 days (CsA/IVMP) vs. 21.5±15.8 (Pred)	Relapse rate 58% (in CsA) vs. 33% (CsA/IVMP) vs. 67% (Pred) (p = NS)	Data not available
RTX					
Fenoglio et al. [58]	Case series of 6 adults (mean age 62.7 years) with de novo MCD treated with RTX	375 mg/m^2×4 weekly doses	CR: 83% (5 out of 6 patients). 1 patient with 75% reduction in proteinuria	No relapses (over 8–36 months follow-up)	

CR, complete remission; CsA, cyclosporine; GC, glucocorticoid; IVMP, IV methylprednisolone; MPA, mycophenolic acid; Pred, prednisone or prednisolone; TAC, tacrolimus; MCD, minimal change disease; RTX, rituximab.

nephrotic patients and depressed T cell function make patients more prone to infection [41]. Most observational studies cite the incidence of infectious complications in MCD from 5 to 15% [26–29]. GC therapy is a major contributor to this infection risk and cumulative GC exposure from multiple relapses increases this risk. Szeto et al. [27] noted a higher incidence of infectious complications in steroid-resistant NS (15%) and frequent relapsers (6%) than nonrelapsing MCD (2.8%, $p = 0.03$), although it is unclear how much is due to the disease itself versus the GC treatment. Notably, Waldman et al. [26] did not find any difference in complications in MCD patients between those treated with daily versus alternate-day steroids. Glenn et al. [42] prospectively followed subjects in the Cure Glomerulonephropathy Network (CureGN) study and found infection-related acute care events were more common among patients with GC exposure versus those without GC exposure at enrollment (50.6 vs. 28.6 infection/100 person-years). Other risk factors for infection included younger age, hypoalbuminemia, and nephrotic range proteinuria.

Musculoskeletal complications: Many of the musculoskeletal adverse effects are likely to occur with recurrent exposure to GC. The incidence of bone avascular necrosis and fracture was higher in frequently relapsing MCD patients than infrequent relapsers (4 vs. 1.1% for AVN, p = NS and 15 vs. 5% for any fracture, $p = 0.006$) [27]. Kyrieleis et al. [36] examined long-term adverse outcomes of frequently relapsing childhood-onset MCD patients who continued to relapse after puberty. These patients frequently developed complications such as hypertension (47%), cataracts (20%), and lumbar spine osteoporosis (33%). Hegarty et al. [43] studied 34 adult survivors of childhood MCD and they were found to have a significant reduction in forearm trabecular bone mineral density (Z score −0.95 and T score −1.04, $p < 0.0001$), placing them at increased fracture risk at this site; these adults also had short stature (height Z score −0.45, $p = 0.007$) and higher BMI (BMI Z score 1.62, $p < 0.0001$) than their age-matched counterparts.

To protect against some of the infectious complications of GC, adults with NS should be vaccinated against encapsulated bacteria such as Pneumococcus per CDC guidelines [44]. Live vaccines should be avoided during and within 4 weeks prior to starting immunosuppression. Prophylaxis against *Pneumocystis jirovecii* pneumonia should be considered if exposed to high-dose GC (≥20 mg of prednisone) for ≥4 weeks [45, 46].

Steroid Minimization Approaches: Induction of Remission

Given the clear concerns regarding the adverse effects of high-dose GC, several approaches to limit the GC dose have been studied, both during the induction phase in achieving remission (Table 4) and in preventing further relapses.

Shorter GC Taper after Induction

After successful induction therapy with high-dose GCs, which occurs in 90% of adults, GC tapering has usually been slow (over 3–6 months) in adults to reduce disease relapse frequency. By contrast, in children, three recent randomized trials demonstrated that a shorter taper (over 4–8 weeks) was safe, did not lead to an increased relapse rate, and is now the standard of care in pediatric MCD [47–49].

In adults, the data are more limited. Ozeki et al. [8] reported a prospective, observational study to evaluate the effectiveness of a 2-month taper in adult steroid-sensitive MCD. In this study, 35 patients with new-onset NS from MCD were initiated on prednisolone at an initial dose of 0.8–1.0 mg/kg/day and continued for 4–6 weeks. The dosage was then reduced to 0.5–0.6 mg/kg alternate days and discontinued after 4 weeks. This short-term steroid group was compared to a historical cohort of 140 adult MCD patients treated with a more extended duration steroid regimen. The relapse rate was not statistically greater in this short-term group versus historical controls (68.8 vs. 53.6%, $p = 0.1$), and there was no difference in frequent relapsers (14.3 vs. 13.6%, $p = 0.91$). Overall, patients treated with the short-term steroid regimen received about half the cumulative dose of prednisolone than patients treated with the conventional regimen (4,199 mg of prednisolone over 24 months of follow-up compared to 8,540 mg of prednisolone over the same period). Despite having a substantial discrepancy in corticosteroid exposure, there were no clear differences in reported adverse events.

With the intention of lowering GC exposure, some adults with MCD now receive a regimen consisting of an initial dose (prednisone 1 or 2 mg/kg/every other day) until 1 week after CR, then the dose is halved for 4–6 weeks, then tapered off over a further 6 weeks, ensuring patients receive a minimum of 16 weeks treatment [50].

Mycophenolate Sodium with Low-Dose Prednisone

Rémy et al. [51] conducted an open-label randomized controlled trial (MSN study) involving 32 French centers with 116 adults with de novo or first relapse of MCD. Par-

ticipants randomly assigned to the test group (n = 58) received low-dose prednisone (0.5 mg/kg/day, maximum 40 mg/day) plus enteric-coated mycophenolate sodium (720 mg twice daily for 24 weeks) versus the control group (n = 58) who received conventional high-dose prednisone (1 mg/kg/day, maximum 80 mg/day) tapered over 24 weeks. Baseline characteristics included a mean age of 44 years, normal renal function (eGFR 87 mL/min), proteinuria (7.9 g/g), and serum albumin 1.6 g/dL.

After 4 weeks of treatment, there was no significant difference between the two groups in the CR rate (64.9 vs. 57.9%, p = 0.44). Secondary outcomes, including CR after 8, 24, and 52 weeks of treatment, also did not differ between the two groups (82.6 vs. 70% at 8 weeks; 80.4 vs. 79.6% at 24 weeks; 67.5 vs. 78.9% at 52 weeks). During 52 weeks of follow-up, relapse rates in both groups were remarkably low (18.75 vs. 27.3%). Serious adverse effects did not differ between the groups.

Tacrolimus Monotherapy

Medjeral-Thomas et al. [50] studied 50 adults with de novo MCD in a multicenter, prospective, open-label trial involving six nephrology units across the UK randomized to tacrolimus (0.05 mg/kg twice daily, target trough 6–8 ng/mL, n = 25) or prednisolone (1 mg/kg daily up to 60 mg daily, n = 25). Twelve weeks after achieving CR, the tacrolimus dose was gradually reduced over 8 weeks and stopped. In the prednisolone group, 1 week after achieving CR, the steroid dose was halved for 4–6 weeks, then gradually reduced and stopped over a further 6 weeks, ensuring patients received a minimum of 16 weeks of prednisolone. The patients' median age was 43 years, and renal function was preserved (mean serum creatinine 0.82 mg/dL) with heavy proteinuria (urine protein creatinine ratio 7.3 g/g) and serum albumin 1.6 g/dL.

There were no significant differences between the prednisolone and tacrolimus treatment groups in CR rates at 8 weeks (84 vs. 68%), 16 weeks (92 vs. 76%), or 26 weeks (92 vs. 88%), but post hoc analysis demonstrated that a higher proportion of patients treated with prednisolone attained CR at 4 weeks (64 vs. 22%, p = 0.005). Relapse rates after achieving CR were high in both groups (74 vs. 73%, p = 0.99), mostly occurring after immunosuppression had been discontinued. Although there were small numbers in this study, tacrolimus monotherapy may be a good option for some patients, although prednisolone resulted in a higher remission rate at earlier time points (4 weeks) and may be preferred in patients with severe NS.

Li et al. [52] conducted a prospective, open-label, multicenter, randomized, controlled trial in eight renal units across China. Patients were randomized to receive oral prednisone (n = 56) or tacrolimus (n = 63) after a 10-day course of intravenous methylprednisolone (0.8 mg/kg per day) in both groups. The initial prednisone dose was 1 mg/kg per day (maximum 80 mg/day) for 6–8 weeks, then tapered over a further 5–6 months. Tacrolimus was initiated at 0.05 mg/kg per day and adjusted to a target trough whole-blood level of 4–8 ng/mL and maintained for 16–20 weeks, then tapered to a trough level of 2–5 ng/mL over 18 weeks until complete withdrawal. The treatment course for both groups was 36 weeks. Remission rates were high in both groups (96.2 vs. 98.3%), and the mean time to remission (2.7 ± 2.3 vs. 2.6 ± 2.6 weeks) was similar between GC-treated and tacrolimus-treated patients. Relapse rates (49.0 vs. 45.5%) and mean time to relapse (24.2 ± 15.4; vs. 23.3 ± 16.9) were similar between the two groups. Adverse events occurred more frequently in the GC group (128 vs. 81 in the tacrolimus group). It should be highlighted that pulse intravenous methylprednisolone treatment was given for 10 days at the beginning of this study in both treatment arms.

Tacrolimus with Low-Dose Corticosteroids

Chin et al. [53] conducted a 24-week, open-label, multicenter, noninferiority trial in 144 Korean adults with MCD (68 de novo and 68 relapsed MCD). They were randomized to receive tacrolimus (0.05 mg/kg twice daily, goal trough 5–10 ng/mL) plus low-dose prednisolone (0.5 mg/kg daily), or standard dose prednisolone (1 mg/kg), for up to 8 weeks or until achieving CR. Two weeks after CR, the steroid dose was tapered to a maintenance dose of 5–7.5 mg/day in both groups, and the tacrolimus dose was lowered to the maintenance dose (goal trough 3–8 ng/mL) until 24 weeks after study drug initiation. CR rates were similar in both groups (79.1 vs. 76.8%) with no difference in time to remission. The relapse rate at 24 weeks was lower in the maintenance tacrolimus plus tapered steroid group (5.7 vs. 22.6%, p = 0.01).

Cyclosporine Induction

There have been few studies on cyclosporine (CsA) monotherapy in adult MCD. Shirai et al. [54] conducted a pilot open-label RCT in Japanese adults (n = 21) with new-onset MCD. Adult new-onset MCD patients were initially treated with prednisolone (0.8 mg/kg) and 2 weeks after achieving proteinuria ≤1 g/day were randomized to CsA (2 mg/kg, goal CsA C2 level 600–1,200 ng/mL) with steroid taper by 4 months versus a prolonged prednisolone taper over 18 months. After 30 months, fol-

Table 5. Steroid minimization approaches in MCD: treatment of relapsing disease

Medication	Evidence	Regimen	Relapse rate	Time to relapse
CYC				
Waldman et al. [26]	Retrospective case series (n = 20) as 2nd line agent. Five patients received concurrent GC at the initiation of CYC	100–150 mg (mean dose 124 mg/day) for 12 weeks	35% relapse rate	Mean time:18 months (6–42)
Fenton et al. [28]	Retrospective observational study in the UK. Oral CYC used in 10 patients (2 SR and 8 FR) as 2nd line agent for 9 weeks	Data not available	60% relapse rate	Median time: 20 months (5–44)
Maas et al. [29]	Retrospective cohort study. Fourteen patients treated with CYC as 2nd line with GC. GC dose was tapered over time. Seven patients received 2 courses of CYC	150 mg (100–200 mg) daily for 13 weeks	64% relapse rate	Data not available
Nolasco et al. [30]	Retrospective case series (n = 36) in relapsing MCD (2 patients as initial therapy). Eleven patients received concurrent GC at the start of treatment and 25 received CYC alone	2–2.5 mg/kg/day for 8–14 weeks	41% relapse rate Follow-up duration 5 years	Data not available
Mak et al. [59]	Retrospective cohort study in FR/SD patients (n = 22). Second course of CYC was given in 6 relapsers	2–2.5 mg/kg for 8 weeks	56% relapse rate in SD patients 20% relapse rate in FR patients	Mean time to relapse 18 months (6–27)
Ponticelli et al. [60]	Open-label RCT in 73 patients with SD or FR MCD (CYC vs. CsA)	2.5 mg/kg/day for 8 weeks	33% relapse rate in FR and 40% relapse rate in SD patients 37% relapse rate at 24 months (60% adults and 32% children)	Data not available
Li et al. [61]	Prospective cohort study in SD MCD. Thirteen patients received CYC and 11 patients received TAC along with prednisone (0.5 mg/kg/day), which was tapered off throughout the study	750 mg/m^2/month IV for 6 months	40% relapse rate in the CYC group Follow-up duration 12–46 months	Data not available
CsA				
Waldman et al. [26]	Retrospective case series (n = 39) as 2nd line agent. Twelve patients received concurrent GC at the beginning	220 mg/day (trough 150–200 ng/mL) for 49.5 weeks	41% relapse rate	Data not available
Maas et al. [29]	Retrospective cohort study. Seven patients with CsA as 2nd line agent in combination with GC	300 (150–400) mg/day for 131 weeks	86% relapse rate	Data not available
Ponticelli et al. [60]	Open-label RCT in 73 patients with SD or FR MCD (CYC vs. CsA)	5 mg/kg/day for 9 months (trough 200–600 ng/mL)	86% relapse rate in FR and 57% relapse rate in SD patients 75% relapse rate in all patients at 24 months (50% adults and 80% children)	Data not available
Eguchi et al. [62]	Prospective open-label RCT in patients with relapsing MCD. Patients randomized to CsA + PSL group (n = 26) vs. the PSL alone (n = 26)	CsA (AUC 1,700–2,000 ng/mL) + PSL (0.8 mg/kg/day) group vs. PSL alone (1 mg/kg/day)	19% relapse rate (CsA + PSL) and 23% relapse rate (PSL only) at 6 months	Data not available
TAC				
Fenton et al. [28]	Retrospective observational cohort. Fifteen patients were treated with CsA and 10 patients treated with TAC as 2nd line agent for 18 months. Three patients had SR and 22 patients had FR MCD	Data not available	64% relapse rate	Median time to relapse: 7 months (2–22)

Medication	Evidence	Regimen	Relapse rate	Time to relapse
Li et al. [61]	Prospective cohort study in SD MCD. Thirteen patients received CYC and 11 patients received TAC along with prednisone (0.5 mg/kg/day), which was tapered off throughout the study	TAC (target trough 4–8 ng/mL) for 6 months	50% relapse rate Follow-up duration 13–43 months	Data not available
Mycophenolate mofetil				
Fenton et al. [28]	Retrospective observational cohort. Six patients treated with mycophenolate as 2nd line agent for 10 months	Variable dosing	50% relapse rate	Median time to relapse: 47 months (25–56)
Pesavento et al. [63]	Four adults with FR MCD after failing CYC therapy	MMF 1,000–1,500 mg daily in divided doses for 19–42 months	25% relapse rate	Data not available
Choi et al. [64]	Retrospective cohort study in 7 adults with CsA- or GC-dependent MCD treated with MMF. 6/7 patients treated concomitantly with GC at the start of therapy and 5 patients were weaned off GC successfully after introduction of MMF. One patient was MMF resistant and subsequently attained CR with TAC	MMF 750–1,000 mg BID for 6–26 months	14% relapse rate	Data not available
RTX				
Fenton et al. [28]	Retrospective observational cohort. Four patients treated with RTX as 2nd line agent	Data not available	No relapse at last follow-up	
Munyentwali et al. [67]	Case series in 17 adults with FR and SD MCD unresponsive to several immunosuppressive agents	375 mg/m^2 1–4 infusions	35% relapse rate 6/17 patients relapsed and remission was reinduced with GC and they again received RTX as GC sparing agent	Mean time to relapse: 11 months (4.8–16.3 months)
Iwabuchi et al. [68]	Prospective cohort study in immunosuppression-dependent MCD (n = 25). RTX was given every 6 months for 24 months. At the end of the 24-month period, patients were divided into treatment continuation (n = 20) or treatment discontinuation (n = 5) according to their intention to continue or discontinue treatment	375 mg/m^2 every 6 month for 4 doses. All 25 patients attained remission after 4 infusions. In the treatment continuation group, RTX was continued every 6 months for 3 additional doses	20% relapse rate in the treatment discontinuation group. No relapses at last follow-up in the treatment continuation group Follow-up duration ~30 months	Data not available
Ruggenenti et al. [69]	Longitudinal, off-on study in 20 adult patients with steroid-dependent or FR NS and 10 children (MCD or FSGS). Patients were in GC-induced remission at the time of RTX administration	1–2 doses of RTX (375 mg/m^2) with tapering of other immunosuppression At 1 year, all patients were in remission: 18 were treatment-free and 15 never relapsed	Relapse rate: 40% (adults), 70% (children), 55% (MCD/MesGN), 38% (FSGS)	Median time to relapse after RTX therapy 7.5 months (0.5–10.7)

MCD, minimal change disease; NS, nephrotic syndrome; GC, glucocorticoid; CsA, cyclosporine; TAC, tacrolimus; RTX, rituximab; CR, complete remission; CYC, cyclophosphamide.

low-up relapse rates were similar between the two groups (63.6 vs. 70%, p = NS).

Matsumoto et al. [55] studied 3 different regimens to treat 26 de novo and 10 relapsed Japanese adult MCD patients in a prospective study. Patients were 35 years old with a UPCR of 6.1 g/day and serum albumin of 2.3 g/dL. Twelve patients were given CsA alone (dose 2–3 mg/kg/day, trough ≤150 ng/mL), and 12 patients received CsA after intravenous pulse methylprednisolone therapy 1,000 mg daily for 3 days (CsA/PMT group). The initial CsA dose was continued for 12 months, then tapered by 25 mg every 2 months. The other 12 patients were given

oral prednisolone (PSL, 40–60 mg/day) alone for 4–6 weeks, followed by daily PSL, with slowly tapering doses. CR was obtained in 75% with CsA alone, 100% with CsA/PMT and 92% with PSL alone ($p = 0.0379$). The median time to remission was shortest in the CsA/PMT group (11.0 ± 5.6 days with CsA/PMT vs. 21.5 ± 15.8 with PSL alone vs. 40.9 ± 35.5 days with CsA). CsA-associated adverse effects were minimal, but more patients in the PSL group had serious adverse effects or cushingoid features.

In general, tacrolimus has a more favorable side effect profile than CsA, and with more familiarity in kidney transplantation, tacrolimus is increasingly preferred for steroid-sparing therapies in MCD. CsA may be preferred in those at high risk for diabetes.

Rituximab Monotherapy

There is interest but limited data on the use of rituximab monotherapy for induction in MCD. In addition to depleting CD20 B cells, rituximab binds directly to podocyte SMPDL3b, leading to direct antiproteinuric effects [13]. Depletion of antigen-presenting B cells by rituximab may restore the balance between autoreactive T cells and regulatory T cells [56] and suppress interleukin-13 secretion by Th2 cells [57]. A role in the suppression of potential autoreactive antibodies is also being investigated in MCD. Fenoglio et al. [58] published a case series of 6 adults (2 male and 4 female, mean age 62.7 years) with de novo MCD who treated with rituximab (375 mg/m^2 times 4 weekly doses) as they had contraindications to steroid therapy. Five of 6 patients (83%) achieved CR and 1 patient had a 75% reduction in proteinuria, although the responses were delayed in 2 patients (>3–6 months). None of the patients relapsed during follow-up of 8–36 months.

Steroid Minimization Approaches: Treatment of Relapsing Disease

Therapies to prevent relapses and avoid recurrent courses of GC in adults include cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, and rituximab (Table 5). Levamisole has been used in the pediatric population, but there is a paucity of literature regarding this drug in adults. Typically, these drugs are given after remission has been induced with GC. Patients often continue low-dose GC concurrently with these agents, and the dose of GC is then tapered over time and discontinued. Cyclophosphamide (commonly 2–2.5 mg/kg/day for 12 weeks) has been studied in observational studies in relapsing disease with a prolonged remission rate of up to 80% in steroid-dependent and frequently relapsing patients [26, 28–30,59–61]. Patients must be counseled regarding the risks of infectious, hematologic, gonadal toxicity, malignancy risk, and repeated doses should be avoided to prevent cumulative toxicity [35]. Calcineurin inhibitors are effective agents to induce remission, and also as maintenance agents to prevent relapses, but are associated with high relapse rates upon discontinuation (~40%) [26, 28, 29, 60–62]. Mycophenolate mofetil has also been used to prevent relapses [28, 63, 64].

More recently, rituximab has been shown to be effective in the prevention of relapses in both children [65, 66] and adults [28, 67–69]. Rituximab is now the standard of care in the pediatric population with steroid-dependent MCD based on the results of these 2 randomized controlled trials. Ravani et al. [65] conducted an open-label, noninferiority RCT in Italian children with steroid-dependent NS. Subjects were randomized to continue prednisone alone ($n = 15$) for 1 month or to add a single intravenous infusion of rituximab (375 mg/m^2, $n = 15$). Prednisone was tapered in both groups after 1 month. The primary outcome of proteinuria at 3 months was 42% lower in the rituximab group (28 vs. 49 mg/m^2/day) which met the noninferiority criteria. The mean prednisone dose at 3 months was lower in the rituximab group than in the control group (0.09 ± 0.21 vs. 0.54 ± 0.39 mg/kg per day). Fourteen of 15 children in the control group relapsed during tapering of the prednisone dose, whereas only 1 child in the rituximab group relapsed within 6 months of randomization. At 1 year, 66% of the children assigned to rituximab were still in steroid-free remission and the median relapse-free time following each infusion was 18 months. Steroid withdrawal was not possible in the control group, and all children required a steroid-sparing agent within a month of attempting the steroid taper. Iijima et al. [66] randomized Japanese children with frequently relapsing or steroid-dependent NS to either rituximab ($n = 24$) at 375 mg/m^2 weekly for 4 doses or placebo ($n = 24$). Children receiving prednisolone for the relapse of NS at screening continued receiving the drug for 4 weeks, and the dose was then tapered. Patients were followed up for 1 year. The primary endpoint of relapse-free period was 73% longer in the rituximab group compared to the placebo group (267 vs. 101 days, HR 0.27, $p < 0.0001$). The time to treatment failure was longer in the rituximab group than in the placebo group (HR 0.27, $p = 0.0005$) and the mean GC dose after randomization was significantly lower in the rituximab group (8.37 vs. 20.02 mg/m^2 per day, $p < 0.0001$). Serious adverse

events were not significantly different (42 vs. 25%, p = 0.36).

In adults, Munyentwali et al. [67] reported a series of frequently relapsing or steroid-dependent adults (n = 17; ages 18–65 years; 13 males, 4 females) with MCD treated with rituximab. All the subjects had failed prior immunosuppressive therapy with different agents and had experienced an average of about 1.3 relapses per year before rituximab therapy. Two-thirds of the patients treated with rituximab had prolonged relapse-free remissions (66%) during an average follow-up of 27 months, and 82% of the patients were able to discontinue other immunosuppressive agents. No significant adverse events were observed. Ruggenenti et al. [69] described 20 adult patients with steroid-dependent or frequently relapsing NS (MCD or focal segmental glomerulosclerosis) who received a single dose of rituximab (375 mg/m^2) with tapering of other immunosuppression. Sixty percent of patients remained relapse-free, and were able to discontinue GC maintenance therapy. These data are encouraging and rituximab is now widely used to prevent MCD relapses in adults. The exact dosing regimen remains unclear, with some choosing a single dose of rituximab 375 mg/m^2, repeating after 1 week if B cell depletion is not achieved (CD19 count <5 cells/mm^3), whereas others choose doses similar to those used in other glomerular diseases (375 mg/m^2, weekly times 4 doses, or 1,000 mg twice, 2 weeks apart).

Conclusion

MCD in adults is typically a steroid-sensitive lesion; however, high doses are needed, therapy is often prolonged, and relapses are frequent. High cumulative exposure to GC may lead to a myriad of adverse effects. Careful dosing and prophylactic therapies may mitigate some of these risks, but minimizing exposure to GC is a goal for both physicians and patients. Fortunately, new data over the last few years show some promising options for minimizing or even avoiding GC, while still maintaining efficacy in the treatment of this disorder. As basic science further progresses our understanding of the pathophysiology and specific pathways underlying MCD, we can expect more targeted therapies in the future, with the promise of even fewer adverse events.

Conflict of Interest Statement

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