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TREATMENT OF MINIMAL CHANGE DISEASE IN ADULTS: CURRENT PRACTICE AND FUTURE DIRECTIONS – A NARRATIVE LITERATURE REVIEW

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ABSTRACT

Research Objectives: This review aims to summarize the current therapeutic strategies for adults with MCD and to discuss future treatment directions in light of emerging immunological and molecular findings.
Methods: Literature was searched using PubMed and Google Scholar, with a focus on studies from the past five years. Keywords used in the search included: „minimal change disease", „nephrotic syndrome", „glucocorticoids", „rituximab", „TRPC6", and „adults".
Key Findings: Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children and a significant contributor in adults. Although its clinical course in adults is often mild and steroid-responsive, many patients experience relapses, steroid resistance, or develop adverse effects related to prolonged glucocorticoid use.
Glucocorticoids remain the first-line therapy for MCD, achieving remission in approximately 90% of adults, but relapses affect more than half of these patients. Alternative immunosuppressive therapies have shown comparable efficacy in inducing remission and may lower the relapse rate. Rituximab has shown significant therapeutic efficacy in steroid-dependent and frequently relapsing cases. Several new pharmacological agents - including TRPC6 inhibitors and ManNAc - are under investigation. Immunomodulatory therapies targeting B and T cells also show promise and are being explored in early-phase studies.
Conclusions: MCD presents ongoing therapeutic challenges due to steroid-related toxicity, and heterogeneous treatment responses. A deeper understanding of the disease's immunopathogenesis is opening new avenues for targeted and safer therapies. Further studies are needed to optimize treatment protocols and improve long-term prognosis and quality of life.

KEYWORDS

Minimal Change Disease, Nephrotic Syndrome, Glucocorticoids, Immunosuppressive Therapy, Novel Therapies, Rituximab

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List of Abbreviations:
AKI - acute kidney injury
CNI - calcineurin inhibitors
CsA - cyclosporine A
CTLA4 - Cytotoxic T-Lymphocyte Antigen 4
CR - complete remission
CYC - cyclophosphamide
eGFR - estimated glomerular filtration rate
FSGS - Focal Segmental Glomerulosclerosis
GCs - glucocorticoids
GR - glucocorticoid receptor
KDIGO - Kidney Disease: Improving Global Outcomes
MCD - Minimal Change Disease
NS - nephrotic syndrome
PCR - protein/creatinine ratio
PD-1 - programmed cell death protein 1
PD-L1 - programmed death ligand 1
PR - partial remission
RCT - randomized controlled trial
RTX - rituximab
TAC - tacrolimus
TRPC6 - transient receptor potential canonical 6

1. Introduction

Minimal change disease (MCD), also known by the less commonly used names lipoid nephrosis or nil disease, is a glomerular disease (glomerulopathy) characterised by normal histopathological findings in light microscopy of kidney biopsies, absence (or slight presence) of IgM or complement C3 deposits on immunofluorescence, and damage to the filtration barrier in the form of diffuse podocyte foot process effacement visible under electron microscopy (Rovin et al., 2021). MCD typically manifests as nephrotic syndrome, the most visible clinical feature of which is edema. The cause is usually idiopathic, although numerous known causes of the secondary form of MCD exist, including neoplasms, allergies, drugs, infections and autoimmune disorders (*Minimal Change Disease - DynaMed*, n.d.; Rovin et al., 2021; Vivarelli et al., 2017; Zamora & Pearson-Shaver, 2025).

MCD is the most common cause of nephrotic syndrome in children, accounting for approximately 70–90% of cases, while in adults, this disease accounts for 10–15% of nephrotic syndrome cases (*Minimal Change Disease - DynaMed*, n.d.; Vivarelli et al., 2017). Its incidence varies depending on the region and ethnic group - in Asian populations, MCD is several times more common in children than in White children (*Minimal Change Disease - DynaMed*, n.d.). Moreover, in Asian adults, MCD accounts for a significantly higher proportion of idiopathic nephrotic syndrome cases (approximately 40%) compared to populations from other regions, as confirmed by studies from Korea and Taiwan (Chang et al., 2009; Huang et al., 2001; Nakagawa et al., 2023). In turn, an analysis of primary glomerulopathies in the United States shows that MCD is diagnosed approximately twice as rarely in Black people as in White people and almost twice as often as in Asians (Sim et al., 2016). Another study found that MCD was significantly less common cause of nephrotic syndrome in Black people than in Asians (26% vs 50.1%), with focal segmental glomerulosclerosis (FSGS) being the most common form (Mbakop et al., 2021).

The pathogenesis of MCD is not fully understood; however growing evidence suggests a complex interaction between immunological and structural factors. Podocytes are specialised epithelial cells that form the outer layer of the filtration barrier, Damage to these cells plays a key role in the disease's pathomechanism, leading to a loss of protein filtration selectivity (Campbell & Thurman, 2022; Chugh & Clement, 2023; Gauckler et al., 2020; Roman & Nowicki, 2024). T-lymphocyte dysfunction, cytokine overexpression (including IL-13) and Treg cell deficiency are considered important elements in the immunopathogenesis of the disease (Roman & Nowicki, 2024). The identification of circulating autoantibodies against nephrin, a key protein of the slit diaphragm, suggests that MCD may have an autoimmune basis in some patients (Watts et al., 2022). Further evidence of the immunological nature of the disease comes from cases of newly diagnosed or relapsing MCD following COVID-19 vaccination. Although a causal relationship has not been clearly

established, systematic reviews authors point to the possible involvement of immune stimulation as a trigger for MCD in predisposed individuals, while emphasising the benefits of COVID-19 vaccination over any potential adverse effects (Kechagias et al., 2024; H. H. L. Wu et al., 2021).

Currently, glucocorticoids (GCs) are the mainstay of treatment for patients with MCD, but therapies targeting the known pathomechanisms of the disease are also under development. The aim of these efforts is to improve treatment efficacy, reduce toxicity and prevent relapsers (Campbell & Thurman, 2022; Roman & Nowicki, 2024; Rovin et al., 2021).

Despite its relatively mild course and high responsiveness to treatment, MCD remains a significant therapeutic challenge, especially in adults. This group of patients is more prone to relapses, steroid resistance and treatment complications, as well as comorbidities that complicate therapeutic management (Campbell & Thurman, 2022; Rovin et al., 2021).

This article reviews current knowledge on treatment methods and their effectiveness for adult patients with MCD, and analyses future therapeutic directions based on known pathogenetic mechanisms of the disease.

2. Methodology

Relevant literature was identified through a review of PubMed and Google Scholar databases using keywords such as „minimal change disease", „nephrotic syndrome", „glucocorticoids", „cyclosporine", „tacrolimus", „rituximab", and „TRPC6". The selection included original studies, clinical trials, and meta-analyses published in English, with a focus on studies from the last five years involving adult patients with MCD.

3. Treatment of MCD

3.1. Glucocorticoids

Glucocorticoids (GCs), such as prednisone and prednisolone, are considered the primary and most conventional first-line treatment for patients diagnosed with minimal change disease, in both children and adults (Koirala & Jefferson, 2021; Rovin et al., 2021).

It was originally thought that their efficacy in treating MCD was due to immunosuppression resulting from the inhibition of the leukocyte-dependent inflammatory response. However, it is now known that this is only one of several possible mechanisms, and that the action of GCs extends beyond classic immunosuppressive properties, particularly through a direct effect on podocyte function (Hodgens & Sharman, 2025; Ransom et al., 2005).

After entering the cell, glucocorticoids act mainly by activating the cytoplasmic glucocorticoid receptor (GR). The GC-GR complex formed in this way is transported to the cell nucleus, where it modulates the expression of numerous genes primarily those responsible for metabolism, inflammation, cell signaling and the immunological response. In the context of MCD, the transactivation of genes encoding proteins with protective and anti-inflammatory effects and the transrepression of pro-inflammatory protein genes, for example by binding and blocking the pro-inflammatory transcription factor NF-κB, are particularly important (Goodwin, 2019; Ponticelli & Locatelli, 2018; Zhao et al., 2018).

Firstly, it has been demonstrated that GCs can stabilise the actin cytoskeleton. In mouse podocyte cultures, dexamethasone was found to protect podocytes and restore the structure of their cell processes following damage caused by cytoskeletal toxins (Ransom et al., 2005). A similar result was obtained in human podocytes after the use of prednisolone. This effect was associated with the inhibition of Rac1 GTPase activity, which led to the stabilisation of the actin cytoskeleton and a reduction in podocyte motility (McCaffrey et al., 2017).

Secondly, the action of GCs on GR appears to be responsible for the increased expression of podocyte structural proteins such as synaptopodin, α-actinin-4, nephrin and CD2AP. These proteins stabilise the filtration slit and protect against the loss of plasma proteins in the urine. Further confirmation of the direct protective effect of GCs on podocytes was provided by a significant increase in proteinuria and damage to podocyte foot processes in mice experimentally deprived of the podocyte-specific glucocorticoid receptor (GR) and subsequently exposed to a glomerular toxin (Zhou et al., 2017).

The third important mechanism is protection against apoptosis. It has been demonstrated that GCs increase the activation of the PI3K/Akt pathway and ERK kinase signaling, thereby regulating the action of numerous transcription factors. This increases the expression of anti-apoptotic proteins, such as Bcl-2, and reduces the level of p53, a protein responsible for inducing apoptosis, thereby limiting the death of podocytes induced by oxidative stress or toxins (Zhao et al., 2018).

Furthermore, glucocorticoids exhibit complex non-genomic effects, bypassing direct regulation of gene expression. These effects are significantly faster than the influence of GCs on gene transcription in the cell

nucleus. They include direct interaction with the cell membrane, e.g., through the specific membrane receptor mGR or with the mitochondrial membrane, as well as direct interactions of GC-GR with cytoplasmic kinases such as JNK (Lin et al., 2022; Ponticelli & Locatelli, 2018).

Despite their effectiveness, the use of GCs is associated with a wide range of adverse effects, the frequency of which increases significantly with high doses of GCS and depends on the duration of their use. Long-term GC use results in metabolic disorders such as hyperglycaemia, abdominal obesity, and hypertension, which significantly increase the incidence of cardiovascular events. Bone complications such as osteoporosis and bone fractures, as well as avascular necrosis, are also common. In turn, suppression of the hypothalamic-pituitary-adrenal axis is a complication that significantly affects the course of therapy and necessitates a slowly reducing GC dose over several months (Hodgens & Sharman, 2025; Ponticelli & Locatelli, 2018). The immunosuppressive effect of glucocorticoids increases susceptibility to infections, including opportunistic infections such as Pneumocystis jirovecii pneumonia, gastrointestinal candidiasis and herpes infections. It may also reactivate latent infections such as viral hepatitis (HBV and HCV), tuberculosis and cytomegalovirus (CMV) infection (Hodgens & Sharman, 2025; Koirala & Jefferson, 2021).

Patients may also experience psychiatric symptoms (insomnia, irritability, psychosis), eye diseases (glaucoma and cataracts), skin changes, and growth retardation in children. Additionally, the use of GCs may be associated with adverse cosmetic effects, such as weight gain, characteristic redistribution of body fat, muscle wasting, skin thinning and acne, which are typical features of Cushing's syndrome (Hodgens & Sharman, 2025).

Furthermore, some patients (especially adults) develop resistance (steroid resistance - SR) or dependence (steroid dependence - SD), which requires alternative or steroid-sparing therapy, such as cyclophosphamide or calcineurin inhibitors (Koirala & Jefferson, 2021).

According to the latest KDIGO guidelines from May 2025, in children with nephrotic syndrome and suspected MCD, it is recommended to start steroid treatment without prior kidney biopsy. The typical regimen for children involves glucocorticoid administered for 8 weeks: 2 mg/kg daily (max. 60 mg/d) for the first 4 weeks, followed by 1.5 mg/kg (max. 40 mg) every other day for the next 4 weeks, or a similarly dosed 12-week regimen (6 + 6 weeks). While most children respond to this initial treatment, the relapse rate is higher than in adults, reaching up to 90% in this group (Floege et al., 2025).

In adults, however, a kidney biopsy is necessary to diagnose MCD and must be performed before immunosuppressive treatment can be initiated. KDIGO recommends starting treatment with prednisone or prednisolone at a daily dose of 1 mg/kg per day (max. 80 mg/day) or 2 mg/kg (max. 120 mg) every other day for 4–16 weeks, until complete remission is achieved. If remission occurs, therapy should continue at the same dose for another 2 weeks, followed by a slow tapering off of the drug over at least 24 weeks (Rovin et al., 2021).

The definitions of terms and the criteria for diagnosing different responses to steroid treatment in patients with MCD differ between adults and pediatric patients. Therefore, this paper focuses on the definitions used in the adult patient group.

The most important terms encountered in clinical practice include (Rovin et al., 2021):

- complete remission (CR) – reduction of proteinuria to <0.3 g per day or a protein/creatinine ratio (PCR) below 300 mg/g (<30 mg/mmol), with a simultaneous plasma albumin concentration >3.5 g/dL and stable creatinine levels – its occurrence during GC monotherapy indicates steroid sensitivity
- steroid resistance - persistent proteinuria >3.5 g/day or protein/creatinine ratio above 3500 mg/g (>350 mg/mmol), with a simultaneous reduction in proteinuria of less than 50% compared to the baseline values despite the use of prednisone in the above-described regimen for a period longer than 16 weeks
- relapse - appearance of proteinuria >3.5 g/day or PCR >3500 mg/g after achieving complete remission
- frequent relapses – ≥2 relapses within 6 months or ≥4 within 12 months
- steroid dependence – relapse during treatment with glucocorticoids or within 2 weeks of its completion.

Although adults generally respond well to glucocorticoids, with complete remission achieved in over 80% of patients, a significant proportion experience relapses. This can lead to repeated cycles of steroid treatment, resulting in an increased risk of adverse effects such as weight gain, hyperglycaemia, hypertension and osteoporosis (Koirala & Jefferson, 2021; Rovin et al., 2021). Patients who are steroid-resistant or experience frequent relapses often require alternative therapies and pose a particular challenge (Rovin et al., 2021).

In light of the above, it is reasonable to evaluate the efficacy and limitations of GC treatment in clinical practice. Below, six studies involving a population of adult patients with MCD are analysed, focusing on the response to GC treatment, the frequency of relapses and adverse effects.

Two glucocorticoids were used in the analysed studies: prednisone, which was used in a study from Greece (Lionaki et al., 2021), and prednisolone, which was used in studies from Pakistan (Shakeel et al., 2024), the United Kingdom (Fenton et al., 2018; Medjeral-Thomas et al., 2020) and India (Udupa et al., 2023); meta-analysis from China (Lu et al., 2022) included publications using both drugs, depending on the standards in force in individual countries.

In a retrospective study from Pakistan involving 21 patients with MCD, 18 patients received steroids as first-line treatment. Within an average of 8 weeks, remission was achieved in 88.88% of patients treated with steroids (including over 50% CR). Four patients treated with steroids as first-line therapy experienced relapse, and the authors showed that these patients had significantly higher blood pressure compared to patients without relapse (Shakeel et al., 2024).

In a retrospective study from the UK, a population of 52 individuals with newly diagnosed nephrotic syndrome in the course of MCD was identified. One individual achieved spontaneous remission, and all other patients received daily glucocorticoid treatment.

Initial remission was achieved in 90% of treated patients, while 10% proved to be steroid-resistant. Overall, after the use of second-line drugs (calcineurin inhibitors or cyclophosphamide), complete remission was achieved in as many as 98% of patients within an average of 5 weeks. However, in this group, 61% of patients experienced relapses, and in 17 (more than half of them), the relapse occurred within 6 months of CR. The relapse rate in the group of 46 patients who achieved CR or PR was also 61%, and re-administration of GCs was effective in all these cases. The authors of this study also showed that higher eGFR values were associated with a significantly higher risk of relapse (Fenton et al., 2018).

In a retrospective study from Greece, in a selected group of 59 patients with adult-onset primary MCD with nephrotic syndrome, 42 patients received steroid monotherapy as first-line treatment. In this study, as many as five patients experienced spontaneous remission and six patients were steroid-resistant. Overall, 88.1% of the patients achieved remission after treatment with various drugs, and relapses occurred in 24 patients, i.e., in approximately 51% of those who achieved remission as a result of treatment. Although the authors did not explicitly report the results for the steroid-sensitive patient group, these values can be calculated from the table included in their paper (Table 4.) – the remission rate with GC monotherapy was 90.5% (CR and PR), and the relapse rate was 55.3%. In addition, the authors showed that relapsers had a significantly longer duration of proteinuria prior to biopsy, less frequent AKI and were younger than those without relapses (Lionaki et al., 2021).

The aim of another study, an RCT from the UK, was to compare the efficacy of two monotherapies, tacrolimus (TAC) and glucocorticoids (GCs), in treating patients presenting for the first time with minimal change disease and nephrotic syndrome. To this end, the of complete remission rates in both groups of 25 patients were compared at 8, 16 and 26 weeks after the start of treatment. In the tacrolimus-treated group, CR was 68% at week 8 and 88% at week 26. In the GCs-treated group, it was 84% and 92%, respectively. Relapses occurred in 74% of steroid-treated patients who achieved CR at week 26 (Medjeral-Thomas et al., 2020).

In an observational study from India conducted in a group of 54 people with diagnosed primary MCD, 52 patients received steroid treatment and two achieved spontaneous remission. According to the authors, 47 patients (87%) achieved remission (CR or PR), and 13% were resistant to steroids. Relapses occurred in 21 patients (38.89%) and required the use of drugs such as calcineurin inhibitors or rituximab (Udupa et al., 2023).

A meta-analysis from China compared the results of four RCTs to determine the efficacy and safety of monotherapy with tacrolimus or steroids in patients with MCD. The meta-analysis showed that GCs were effective in inducing complete remission in 84.2% of patients with newly diagnosed MCD with nephrotic syndrome. Although incomplete, data from individual studies show that steroids enabled total remission in approximately 89% of patients, with relapses occurring in 46% of those treated with GCs. In addition, the authors demonstrated no significant differences in efficacy and complication rates between tacrolimus and steroids (Lu et al., 2022).

All cited studies highlight the frequent complications associated with chronic steroid therapy. In retrospective studies from the UK and Greece, an increased risk of infection and diabetes was observed, emphasising the need for metabolic monitoring. Other commonly reported adverse effects included hyperglycaemia, weight gain, venous thromboembolism, reduced bone mineral density resulting in fractures, acne, cataracts and mood disorders. Another frequently mentioned complication in the course of MCD was AKI, which can pose a serious threat to the patient's health and requires more careful selection of drugs (Fenton et al., 2018; Lionaki et al., 2021; Lu et al., 2022; Medjeral-Thomas et al., 2020; Shakeel et al., 2024; Udupa et al., 2023).

3.2. Calcineurin Inhibitors

Cyclosporine (CsA) and tacrolimus (TAC) are drugs that work by inhibiting calcineurin, a calcium- and calmodulin-activated phosphatase, which leads to the blocking of NFAT transcription factor activation and a decrease in interleukin-2 production. In this way, they inhibit the activation and proliferation of T lymphocytes, stabilise the cytoskeleton of podocytes and reduce damage to the filtration membrane in the glomeruli (Lu et al., 2022; Patil et al., 2019; Prasad et al., 2018).

In a randomised study by Chin et al., it was demonstrated that in the treatment of adults with MCD and nephrotic syndrome, tacrolimus in combination with low-dose prednisolone was equally effective in inducing complete remission (79.1% vs 76.8% at 8 weeks of treatment) as prednisolone monotherapy at a standard dose of 1 mg/kg, but was associated with a significantly lower relapse rate and fewer metabolic complications (Chin et al., 2021). For comparison, in a randomised UK study comparing prednisolone monotherapy with tacrolimus, no significant differences in the incidence of remission and relapse were found, but it was shown that the steroid led to remission faster than tacrolimus (Medjeral-Thomas et al., 2020).

Furthermore, in a prospective, multicentre study of tacrolimus monotherapy after prior short-term (10-day) intravenous methylprednisolone treatment, tacrolimus was shown to be non-inferior to glucocorticoids in terms of remission induction (98.3% vs 96.2%), and its use was associated with a significantly lower incidence of frequent relapses and adverse events (including serious ones) (X. Li et al., 2017).

The fact that tacrolimus is comparable to steroids in its efficacy in inducing remission is also confirmed by other studies, such as a meta-analysis by Lu et al. from China and a randomised controlled trial by Patil et al. with long-term (18 months) follow-up of treated patients, in which the last follow-up showed a total remission rate of over 40% in both study groups (Lu et al., 2022; Patil et al., 2019).

In turn, a comparison of the efficacy and safety of calcineurin inhibitors in a pediatric group was presented by Prasad et al. In their prospective analysis of patients resistant to steroids and cyclophosphamide, they demonstrated a higher remission rate in the tacrolimus-treated group (81.8%) compared to cyclosporine (69.5%) with a significantly lower incidence of complications in the TAC group (Prasad et al., 2018).

The use of calcineurin inhibitors is associated with the risk of adverse effects typical of this group of drugs, including hypertension, hyperglycaemia, renal function impairment and neurotoxicity. Long-term treatment with cyclosporine was more associated with hypertension, hypertrichosis and gingival hyperplasia, while tacrolimus more frequently caused tremors, glycaemic disorders and diarrhoea (Prasad et al., 2018). Compared to steroids, CNIs do not cause metabolic and bone complications typical of GCs, but require careful monitoring of kidney function and serum drug concentrations to minimise the risk of nephrotoxicity (Chin et al., 2021; X. Li et al., 2017; Lu et al., 2022; Medjeral-Thomas et al., 2020).

The authors of the analysed publications agree that tacrolimus and cyclosporine are important therapeutic alternatives to classic first-line steroid therapy, particularly in relapsing or steroid-resistant cases (Chin et al., 2021; X. Li et al., 2017; Lu et al., 2022; Medjeral-Thomas et al., 2020; Patil et al., 2019). Compared to cyclophosphamide, CNIs have a better safety profile in terms of gonadotoxicity, long-term neoplastic complications and infections, and compared to rituximab, they have better availability and a simpler oral administration route, as confirmed by meta-analyses and clinical studies (Lan et al., 2024; Ren et al., 2013).

3.3. Cyclophosphamide

Cyclophosphamide (CYC) is an alkylating agent belonging to the group of cytostatic drugs, whose metabolites act by forming cross-links between DNA strands, leading to apoptosis of proliferating lymphocytes. In a nephrological context, its efficacy is mainly attributed to its immunosuppressive effect, which involves the elimination of T and B lymphocytes responsible for podocyte dysfunction (Ogino & Tadi, 2025). In the treatment of MCD, it is primarily used in adult patients with relapsing or steroid-dependent nephrotic syndrome, and as an alternative in cases of glucocorticoid intolerance (“Chapter 5, ” 2012; Ponticelli et al., 1993; Rovin et al., 2021).

Data from the analysed studies indicate that cyclophosphamide has comparable efficacy in inducing remission to steroids and calcineurin inhibitors, but its use was associated with a significantly lower relapse rate and a higher percentage of sustained remissions compared to steroid treatment (“Chapter 5, ” 2012; Rovin et al., 2021). In contrast, CYC was less effective than cyclosporine in inducing durable remissions in adults (50% vs. 40% at 2 years), which contrasted sharply with the opposite trend in the pediatric group – 20% vs. 68% in favour of cyclophosphamide (Ponticelli et al., 1993). Furthermore, a Chinese study comparing the efficacy of tacrolimus and intravenous cyclophosphamide in steroid-resistant patients with MCD showed lower

efficacy of CYC and a significantly longer time to remission than in the tacrolimus-treated group (H. Li et al., 2012).

In a retrospective study from Greece involving patients with nephrotic syndrome due to MCD, cyclophosphamide in combination with low-dose prednisone was used both as initial treatment (11% of those treated) and more frequently as second-line therapy, mainly in patients with relapses after GC treatment (Lionaki et al., 2021). Cyclophosphamide as a first-line treatment resulted in a high remission rate, but the authors did not provide final data on the efficacy of CYC. However, it was shown that the frequency of relapses in patients treated with cyclophosphamide was similar to that in patients who received steroid monotherapy as first-line treatment. Similar results demonstrating the efficacy of cyclophosphamide in inducing remission were reported in studies from Pakistan and the UK, where this drug was administered to patients experiencing relapses after steroid therapy (Shakeel et al., 2024) as well as to steroid-resistant patients (Fenton et al., 2018).

Cyclophosphamide is a drug with a well-known profile of adverse effects. The most common include myelosuppression, nausea, alopecia, haemorrhagic cystitis and an increased risk of infection. In addition, treatment is associated with a risk of fertility disorders, such as azoospermia or menstrual disorders, as well as an increased risk of developing secondary neoplasms with long-term or repeated treatment (Ogino & Tadi, 2025; Ren et al., 2013). To minimise the toxic effects of cyclophosphamide, prophylactic measures such as adequate hydration, administration of mesna and regular monitoring of blood counts and liver and kidney function are recommended (Ogino & Tadi, 2025).

3.4. Rituximab

Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, originally approved for the treatment of lymphoproliferative malignancies, has found application in the treatment of nephrological diseases, including minimal change disease. Its action is based not only on B-cell depletion, but also on the stabilisation of the actin cytoskeleton of podocytes through interaction with the enzyme protein SMPDL-3b, which may prevent the loss of podocyte slit diaphragm integrity (Aslam & Koirala, 2023; Gauckler et al., 2020; Xue et al., 2020).

Both individual studies and meta-analyses confirm the high efficacy of rituximab in adult patients with relapsing or steroid-dependent MCD.

In a retrospective study from China involving 81 adults with frequently relapsing or steroid-dependent nephrotic syndrome, the use of rituximab enabled the discontinuation of steroids in approximately 70% of patients and led to a decrease in the number of relapsers (Lan et al., 2024).

In a meta-analysis by Hansrivijit et al., involving 11 studies of adults with MCD, the overall efficacy of rituximab in achieving remission in this group was 80.3%, with less than 40% of patients experiencing a relapse (Hansrivijit, Cheungpasitporn, et al., 2020). Comparable results were obtained in a meta-analysis by Xue et al., in which the efficacy of RTX in inducing complete remission in MCD patients was over 90% and the relapse rate did not exceed 30%. The authors suggested that such favourable results may be due to the advantage of prospective studies with shorter follow-up times (Xue et al., 2020).

For example, Takei et al., in their prospective study of 25 adult patients with steroid-dependent MCD, showed that a single dose of rituximab resulted in final remission in 100% of patients, with approximately 23, 5% experiencing relapsers (Takei et al., 2013).

Rituximab has been particularly effective in patients with steroid-dependent or frequently relapsing MCD, especially in cases where other therapeutic options (cyclophosphamide, calcineurin inhibitors) did not result in long-term remission or cause complications. In addition, the authors emphasise the beneficial effect of rituximab in reducing proteinuria and steroid doses in patients with MCD (Aslam & Koirala, 2023; Fenton et al., 2018; Gauckler et al., 2020; Hansrivijit, Cheungpasitporn, et al., 2020; Lan et al., 2024; Xue et al., 2020).

Rituximab was well tolerated in all studies analysed, and serious complications were very rare. The most common adverse reactions were various types of transient post-infusion reactions (chills, rash, hypotension) and lymphopenia, less frequently neutropenia and infections, and these complications rarely led to discontinuation of therapy (Gauckler et al., 2020; Hansrivijit, Cheungpasitporn, et al., 2020; Xue et al., 2020).

3.5. Mycophenolate Mofetil

Mycophenolate mofetil (MMF) acts by inhibiting inosine monophosphate dehydrogenase (IMPDH), a key enzyme in purine synthesis in T and B lymphocytes, resulting in inhibition of their proliferation and induction of apoptosis (Allison & Eugui, 2000). In addition, MMF has a direct protective effect on podocytes by stabilising the actin cytoskeleton and restoring calcium signaling balance, as confirmed in a study in mice with induced nephritis (Hackl et al., 2023).

A retrospective study in adult patients with steroid-dependent or frequently relapsing MCD showed that MMF used for 12 months led to complete remission in 83% of patients, of whom 70% maintained sustained remission until the end of follow-up. Such good results indicate high efficacy in inducing long-term remission in this group of patients and may be due to the carefully selected study population, which excluded steroid-resistant patients (Rathore et al., n.d.).

Furthermore, in a retrospective study from the United Kingdom, MMF emerged as an effective therapeutic option in patients previously treated with steroids, confirming its role as a steroid-sparing second-line drug. In addition, data from this study indicate a longer time to relapse after MMF treatment compared to calcineurin inhibitors and cyclophosphamide (Fenton et al., 2018).

3.6. Alternative Therapies

In some clinical situations, especially in patients with treatment resistance or frequent relapses, other less popular immunosuppressive drugs are used. Although their role is secondary to established first-line therapies, some of them have shown efficacy in small studies or retrospective analyses.

Azathioprine is a classic immunosuppressive drug from the purine analogue group (it disrupts DNA synthesis) that has been used in the past in patients with steroid-resistant MCD. Although its use has been shown to lead to frequent and long-lasting remissions in this group of patients, the efficacy of this treatment remains poorly documented and the quality of available data is limited (Cade et al., 1986). This drug is associated with a risk of adverse effects such as myelosuppression, hepatotoxicity, infections, nausea and rashes. Careful monitoring of blood counts and liver function is required. In addition, azathioprine interacts with allopurinol and other substances that affect purine metabolism, which may increase its toxicity (Mohammadi & Kassim, 2025).

Saquinavir, an HIV protease inhibitor, has been evaluated positively in a pilot clinical trial in patients with steroid-resistant and steroid-dependent MCD. The addition of saquinavir to low doses of calcineurin inhibitors resulted in remission in most of the patients studied. Although these patients later experienced relapses, saquinavir treatment led to a decrease in proteinuria and reduced glucocorticoid doses (Coppo et al., 2012).

Abatacept is a fusion protein containing a fragment of CTLA-4, which, by binding to CD80, prevents costimulation dependent on the corresponding receptor (CD28) on T-lymphocytes. In a systematic review, Hansrivijit et al. reported remission in approximately 44% of patients with diagnosed FSGS or MCD, and its efficacy was significantly higher in patients expressing B7-1 (CD80) on podocytes (confirmed by staining in kidney biopsy). According to the authors, this suggests the possibility of using abatacept in this group of patients (Hansrivijit, Puthenpura, et al., 2020).

Among the less conventional methods of treating minimal change disease, particularly in Asian studies, Tripterygium wilfordii, a plant used in traditional Chinese medicine, plays an important role. Its main active ingredient, triptolide, has strong immunosuppressive and anti-inflammatory effects, including inhibition of T and B lymphocyte activation and inhibition of pro-inflammatory cytokine expression and the NF-κB pathway (Hou et al., 2019; Yuan et al., 2019). A review of randomised clinical trials reported the efficacy of preparations containing Tripterygium triptolide glycosides in the treatment of nephrotic syndrome, but the quality of many analyses was limited (Zhang et al., 2018).

Due to the risk of significant adverse effects, such as hepatotoxicity, myelosuppression and fertility disorders, the use of this plant outside China is limited (Hou et al., 2019; Yuan et al., 2019). Given these risks, additional well-conducted clinical studies are necessary to more accurately evaluate the safety and therapeutic potential of Tripterygium wilfordii in MCD, and to investigate less toxic analogues of its main active compound.

3.7. New Therapeutic Possibilities

In recent years, there has been growing interest in new immunomodulatory therapies that could be an alternative to classic immunosuppressive drugs in the treatment of MCD. Researchers have focused on drugs that target B lymphocytes, including those with mechanisms different from the rituximab used to date. Their use remains experimental, but preliminary data suggest potential, especially in patients with relapsed, steroid-dependent or refractory MCD.

Telitacicept is a fusion protein that combines the TACI receptor with the immunoglobulin IgG Fc fragment. Unlike rituximab, which eliminates mature B lymphocytes with the CD20 marker, telitacicept acts

at an earlier stage of their development by inhibiting the activation and maturation of B cells by blocking the binding of BAFF and APRIL ligands.

In a single clinical report, a combination of telitacicept and prednisone led to complete remission within 4 weeks in a patient with long-standing steroid dependence who had not responded to previous therapy with prednisone and tacrolimus (S. Li et al., 2023). Importantly, studies in other glomerulopathies, such as membranous nephropathy and IgA nephropathy, have also shown its beneficial effect on proteinuria reduction and disease control (S. Chen et al., 2025; L. Wu et al., 2023). These observations indicate the potential efficacy of telitacicept in the treatment of MCD, although further clinical studies, including randomized controlled trials, are needed.

A similarly targeted but differently acting drug is obinutuzumab, a second-generation anti-CD20 monoclonal antibody with greater affinity for B lymphocytes and the ability to induce stronger cellular cytotoxicity than rituximab. It has been used effectively in a single dose in pediatric patients with frequently relapsing or steroid-dependent nephrotic syndrome in whom rituximab proved ineffective. In a retrospective study by Dossier et al., 92% of patients in this group were in remission at 12 months of follow-up, and the remission rate at 24 months was 68%. Obinutuzumab was generally well tolerated, with the most common adverse reactions being transient neutropenia and mild infusion-related reactions (Dossier et al., 2023). These results indicate its usefulness in cases of resistance to rituximab, although further studies are needed, particularly in the adult population.

Multiple less known mechanisms have been identified in preclinical models and theoretical concepts of MCD pathogenesis that may represent future therapeutic targets.

One of these is reduced glycosylation of podocyte-associated proteins, especially angiopoietin-like 4 (ANGPTL4), found in patients with MCD. Studies in animal models have shown that re-sialylation of ANGPTL4 with N-acetyl-D-mannosamine (ManNAc) leads to a reduction in proteinuria by improving the surface charge of filtration slits (Chugh et al., 2012). This observation opens up the prospect of using ANGPTL4 glycosylation modulation as a potential maintenance therapy for remission in patients with MCD. A clinical trial evaluating the efficacy of this therapeutic strategy in humans is currently underway (NCT02639260) (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2023).

Another potential therapeutic target is dynamin, a protein involved in maintaining the structure of the podocyte cytoskeleton and slit diaphragm (through interactions with nephrin). Importantly, in animal models of glomerulopathy, increased dynamin expression was observed to precede the onset of proteinuria, which may indicate its compensatory role in response to filtration barrier damage. Studies have shown that the use of dynamin-stabilising compounds such as Bis-T-23 significantly reduced proteinuria in rodents and restored normal cytoskeletal architecture and cell adhesion in podocytes isolated from patients with FSGS (Khalil et al., 2019; Müller-Deile et al., 2016). These findings suggest the potential use of these or similarly acting substances as a treatment for MCD.

Some patients with MCD have increased activity of tumour necrosis factor alpha (TNF-α) in the kidney, which corresponds to higher proteinuria and faster loss of kidney function. Therefore, Trachtman et al. decided to investigate the effect of adalimumab (an anti-TNF-α antibody) on the concentration of urinary markers of intrarenal TNF-α activation, MCP-1 and TIMP-1. For this purpose, patients with FSGS or treatment-resistant MCD with elevated levels of these markers were selected.

Although the results were inconclusive, the authors demonstrated that patients with the best preserved kidney parenchyma showed a better response to treatment as assessed by urinary biomarkers. In addition, they emphasised the importance of selecting patients who have reversible disease progression and could benefit from treatment with adalimumab (Trachtman et al., 2024). If this strategy proves effective, it could also be used in the treatment of MCD.

One of the known pathomechanisms of MCD development confirmed in studies is the disruption of immune homeostasis dependent on regulatory T cells (Treg). In kidney biopsies from patients with MCD, a significant increase in the population of Th17 lymphocytes and cytotoxic lymphocytes was found, with a simultaneous decrease in the number of Foxp3 Treg cells. Therefore, immunological interventions aimed at restoring the balance between these cell populations may be beneficial. (L. Liu et al., 2011; Salcido-Ochoa et al., 2017). For example, drugs that promote Treg expansion, such as efavaleukin alfa, could be used in the treatment of MCD, but this hypothesis needs to be verified in future preclinical and clinical studies.

Immune checkpoint modulators (PD-1/PD-L1) are also being experimentally investigated. The interaction of these proteins, through the activation of caspase-3, is responsible for the occurrence of programmed cell death by apoptosis. Increased PD-1 expression on podocytes has been demonstrated in animal

models with ageing or damaged podocytes, as well as in kidney biopsies from patients with FSGS. Based on this observation, the authors of the study used anti-PD-1 antibodies in mice with induced FSGS, which led to a significant increase in the number and health span of podocytes. This strategy, based on increasing the survival of immune cells that eliminate cancer cells, has already proven effective in treating various neoplasms (R. Chen et al., 2024; Pippin et al., n.d.). Its application in clinical practice would expand the range of therapeutic options for podocytopathies such as MCD and FSGS.

MicroRNAs are small non-coding single-stranded RNA molecules consisting of 21-23 nucleotides, whose role is to regulate the expression of other genes. Numerous studies are currently underway on the effect of miRNA on the regulation of podocyte protein expression in MCD, in which both miRNA with a protective effect on podocytes (miR-499) and those that lead to increased apoptosis of damaged cells (miR-27b) have been identified. Furthermore, it has been suggested that miR-150 may be used to differentiate MCD from other nephropathies (F. Liu et al., 2022). The development and practical application of drugs modulating miRNA activity in podocytes may enable more precise control over the course of minimal change disease.

The possibility of using TRPC6 modulators in the treatment of MCD also seems interesting. The TRPC6 channel (Transient Receptor Potential Canonical 6) is a calcium channel located, among others, in the cell membrane of podocytes, playing an important role in maintaining the integrity of the glomerular filtration barrier. Physiologically, it is activated by diacylglycerol (DAG), but it can also be activated by other substances, such as hyperforin or angiotensin II, which leads to the influx of Ca^{2+} ions into the cytoplasm of the podocyte cell (Ma et al., n.d.; Saqib et al., 2023; Scheuble et al., 2020).

The effect of abnormal intensification of this process is the reorganisation of the actin cytoskeleton, activation of proteolytic enzymes such as calpain, and, consequently, podocyte foot process retraction, loss of connections with the basement membrane and the development of proteinuria (Ma et al., n.d.; Scheuble et al., 2020). Excessive TRPC6 activity has been described in various kidney diseases, including FSGS, diabetic nephropathy, lupus nephropathy and MCD, as well as in disorders affecting other organs, such as certain types of cancer (Ma et al., n.d.; Saqib et al., 2023; Schlöndorff & Pollak, 2006).

On the other hand, TRPC6 in different organs, particularly in the central nervous system, plays a beneficial role by participating in the regulation of synaptic plasticity and protecting against damage resulting from ischaemia. For this reason, new drugs targeting TRPC6 could be used in selected patients with high TRPC6 expression in podocytes and no contraindications, and should be highly selective for podocytes (Saqib et al., 2023).

In order to protect podocytes from apoptosis, restore nephrin expression and reduce proteinuria, substances designed to block TRPC6 have been developed. Among the latest molecules of this type is BI-764198, a selective TRPC6 inhibitor that has already been clinically tested in phase 1 trials in populations of healthy adults (Schultz et al., 2025, p. 1; Yonemura et al., 2025). A Phase 2 study to determine the efficacy, safety and properties of BI 764198 in a group of adult patients with FSGS has also recently been completed, with results not yet published (Trachtman et al., 2023). Although it has not yet been evaluated as a treatment for MCD, its protective effect on podocytes and good tolerability suggest that it may also be useful in this disease.

4. Discussion

Minimal change disease is the most common cause of nephrotic syndrome in children and has been relatively well described in this patient group. However, there is still a lack of well-designed large-scale studies that would precisely define risk groups, population differences, and the efficacy and appropriate target group for different therapies in adult patients with MCD (Floege et al., 2025).

Glucocorticoids, the most commonly used first-line treatment for MCD, have a multi-level protective effect, including stabilisation of the podocyte cytoskeleton, increased expression of structural proteins, protection against apoptosis, non-genomic effects and inhibition of pathogenic pathways (Goodwin, 2019; Lin et al., 2022; McCaffrey et al., 2017; Ponticelli & Locatelli, 2018; Ransom et al., 2005; Zhao et al., 2018; Zhou et al., 2017).

The analysed studies have shown that glucocorticoid monotherapy as first-line treatment in adult patients with MCD is highly effective in inducing initial remission, achieving remission in approximately 87-92% of patients (Fenton et al., 2018; Lionaki et al., 2021; Lu et al., 2022; Medjeral-Thomas et al., 2020; Shakeel et al., 2024; Udupa et al., 2023). However, the high relapse rate, the higher incidence of steroid resistance than in children, and long-term side effects pose a serious therapeutic challenge, which is associated

with frequent use of second-line drugs and alternative therapies (Hodgens & Sharman, 2025; Koirala & Jefferson, 2021; Vivarelli et al., 2017).

In the studies discussed, there were cases of spontaneous remission, but their frequency was relatively low (<9%). The studies cited in this publication did not have control groups of MCD patients who did not undergo therapy, so it is uncertain how many treated patients could ultimately achieve spontaneous remission, the frequency of which is estimated in the literature to be as high as 60-70%. Interestingly, no relapses were observed in patients who achieved spontaneous remission (Colattur & Korbet, 2000; Fenton et al., 2018; Lionaki et al., 2021; Shakeel et al., 2024; Udupa et al., 2023). This suggests the possibility of investigating the mechanisms responsible for disease subsiding in individuals with early-onset spontaneous remission.

In the cited publications, steroid-resistant patients accounted for approximately 8-13% of those treated with GCs, which is comparable to data available in older literature (Colattur & Korbet, 2000; Fenton et al., 2018; Lionaki et al., 2021; Lu et al., 2022; Medjeral-Thomas et al., 2020; Shakeel et al., 2024; Udupa et al., 2023; Vivarelli et al., 2017). The relapse rate of 55%-74% in studies from the UK and Greece is also comparable. However, the relapse rates after steroid treatment in studies from Pakistan, India and in a meta-analysis from China were significantly lower than the previously observed 56-80% (Colattur & Korbet, 2000; Fenton et al., 2018; Lionaki et al., 2021; Lu et al., 2022; Medjeral-Thomas et al., 2020; Shakeel et al., 2024; Udupa et al., 2023; Vivarelli et al., 2017). A particular example is the study by Shakeel et al., in which the relapse rate was exceptionally low, affecting 25% of patients who achieved remission, which was probably due to the short follow-up period and the small study group (n=21) (Shakeel et al., 2024).

Following the comparison of response rates, it is worth noting that Udupa et al. reported only 52 of 54 patients received steroid therapy, yet classification was applied to the entire cohort. As two patients reportedly achieved spontaneous remission, this may have slightly affected the accuracy of reported response rates (Udupa et al., 2023).

Studies conducted in a group of pediatric patients with nephrotic syndrome indicate the key role of genetic differences in the course of treatment – for example, polymorphisms of the glucocorticoid receptor (NR3C1) or negative regulator GR (FKBP5) increase the incidence of phenomena such as steroid dependence and relapses, and some variants of the IL-6, TNF-α and P-glycoprotein genes are responsible for steroid resistance (Schijvens et al., 2019). Taking into account the risk factors for such phenomena and monitoring treatment complications are crucial for improving the prognosis and quality of life of patients. In the future, drugs with a better safety profile, such as tacrolimus or rituximab, may become more important in the treatment of MCD, especially in groups of patients at high risk of relapse and steroid side effects (Chin et al., 2021; Hansrivijit, Cheungpasitporn, et al., 2020; Lan et al., 2024; X. Li et al., 2017; Lu et al., 2022; Medjeral-Thomas et al., 2020; Patil et al., 2019; Takei et al., 2013; Xue et al., 2020).

Calcineurin inhibitors are an important group of drugs in the treatment of minimal change disease in adults, characterised by high efficacy in inducing remission and a better safety profile in selected patient groups compared to long-term use of glucocorticoids (Chin et al., 2021; Lu et al., 2022; Medjeral-Thomas et al., 2020; Patil et al., 2019). Although available data seem to indicate a slight advantage of tacrolimus over cyclosporine, there are currently insufficient studies directly comparing the efficacy of tacrolimus and cyclosporine in the treatment of minimal change disease in adults, indicating the need for further well-designed clinical trials in this patient group (Prasad et al., 2018).

Numerous studies confirm the benefits of CNIs, including efficacy comparable to GCs and a good safety profile, while emphasising the need for further observation for long-term complications and optimisation of treatment regimens (Chin et al., 2021; X. Li et al., 2017; Lu et al., 2022; Medjeral-Thomas et al., 2020; Patil et al., 2019; Prasad et al., 2018).

Cyclophosphamide appears to induce remission as effectively as cyclosporine, but its advantage is a potentially longer therapeutic effect and a lower risk of relapse after treatment. However, there are no randomised controlled trials or large retrospective studies that would allow for a clear determination of the efficacy of CYC in adult patients with MCD (Rovin et al., 2021). Unlike calcineurin inhibitors, which often require long-term administration and are associated with a risk of nephrotoxicity, CYC is usually used in limited cycles. However, it should be noted that due to its alkylating action, its long-term use is associated with a risk of gonadal damage and the development of secondary malignancies (Ogino & Tadi, 2025; Ren et al., 2013).

A high remission rate, often exceeding 80%, has been observed in patients treated with rituximab. In many cases, this therapy has allowed for the reduction or complete withdrawal of glucocorticoids and other immunosuppressive drugs. In addition, rituximab significantly reduced the frequency of disease relapses,

which translated into improved quality of life for patients and reduced the need for hospitalisation and retreatment (Aslam & Koirala, 2023; Fenton et al., 2018; Gauckler et al., 2020; Hansrivijit, Cheungpasitporn, et al., 2020; Lan et al., 2024; Xue et al., 2020).

RTX had a good safety profile, with few and usually mild adverse effects, which was an important argument for its use in patients with multiple comorbidities or steroid intolerance (Gauckler et al., 2020; Hansrivijit, Cheungpasitporn, et al., 2020; Xue et al., 2020).

Therefore, rituximab may be a valuable therapeutic option as a second-line treatment in MCD, especially in patients at high risk of adverse effects after long-term steroid therapy, steroid-resistant patients, and patients with frequent relapses.

A meta-analysis by Hansrivijit et al. showed significant differences in response to rituximab between patients with FSGS and MCD. They concluded that patients with minimal change disease may achieve significantly better benefits from rituximab, confirming the importance of proper differentiation between these two diseases (Hansrivijit, Cheungpasitporn, et al., 2020). Shakeel et al. in their analysis of MCD patients from Pakistan, in which they emphasised the importance of high-quality pathomorphological diagnostics in the correct diagnosis of MCD (Shakeel et al., 2024), and a study by Fenton et al. showed that this has a significant impact on the choice of effective therapy – in 5 patients who required second-line treatment with CNI, FSGS was ultimately diagnosed. Such patients were significantly more resistant to steroid treatment and had a longer time to remission (Fenton et al., 2018). The use of accurate diagnostic criteria in the evaluation of kidney biopsies by qualified specialists, and possibly also the use of artificial intelligence algorithms for this purpose, could minimise the risk of false positive diagnoses of MCD, especially in the early stages of FSGS.

To date, numerous pathomechanisms of MCD development have been identified and targeted treatment methods have been proposed, but there is still a lack of research enabling a comprehensive and practical combination of the acquired knowledge to create a complete picture of the pathogenesis and development of this disease (Roman & Nowicki, 2024). Such an in-depth understanding of the relationships and connections between all known pathways could allow for the selection of the most effective therapies or the development of completely new drugs that interrupt key pathways in the development of MCD, and perhaps even prevent the development of the disease in individuals predisposed to it.

5. Conclusions

Although the course of minimal change disease is usually mild and the prognosis is favourable, its clinical importance - as the most common cause of proteinuria in children and one of the leading primary glomerulopathies in adults - has led to extensive research aimed at identifying its underlying causes, elucidating its pathomechanisms, and developing effective treatment strategies. Thanks to these discoveries, the complex nature of MCD has been partially understood, enabling the introduction of more effective treatment regimens, as well as the development of new drugs or the repurposing of existing ones in cases where standard glucocorticoid therapy fails to achieve satisfactory outcome – durable complete remission of MCD. Although these new therapies show great promise, particularly in patients with relapsing, steroid-dependent, or steroid-resistant disease, they are not always effective and may sometimes lead to serious adverse effects. Therefore, it remains essential to optimise current treatment strategies, continue the search for novel therapies, and address the remaining gaps in our understanding of MCD pathogenesis.

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