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REVIEW

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Emerging role of Rituximab in adult minimal change disease: a narrative review of clinical evidence, biomarkers and future perspectives

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Abstract

Minimal change disease (MCD) represents a significant cause of nephrotic syndrome in adults, traditionally managed with corticosteroids despite substantial relapse rates. This review critically evaluates the emerging role of rituximab (RTX) in adult MCD management, synthesizing current evidence across multiple clinical scenarios. Recent studies demonstrate RTX's multifaceted efficacy, particularly in new-onset cases and steroid-dependent/frequently relapsing patients, with the discovery of anti-nephrin antibodies providing unprecedented insights into MCD pathogenesis. RTX's therapeutic mechanisms involve anti-nephrin antibody depletion, T-cell subset modulation, and direct podocyte protection, showing encouraging complete remission rates and substantially reduced relapse rates. While RTX offers a more favorable safety profile compared to long-term corticosteroid therapy, current evidence remains predominantly based on retrospective studies with limited sample sizes. Critical research priorities include large-scale prospective trials, standardization of treatment protocols, and further investigation of anti-nephrin antibodies as therapeutic targets. This review provides evidence-based insights for clinical decision-making while highlighting crucial areas for future investigation in RTX-based MCD management.

Keywords Minimal change disease, Nephrotic syndrome, Rituximab, Anti-nephrin antibodies, B-cells

Background

Minimal change disease (MCD) is a significant cause of nephrotic syndrome in adults, accounting for approximately 10–15% of idiopathic cases [1, 2]. While light microscopy reveals normal glomerular structure, electron microscopy demonstrates extensive podocyte damage, characterized by diffuse foot process effacement and loss of slit diaphragms, without electron-dense deposits [3]. Previous research has established that T-cell dysfunction plays a fundamental role in MCD pathophysiology. During disease activity, patients exhibit characteristic immunological alterations, including a reduction in regulatory T cells (Tregs), an increase in T helper cells (Th1 and Th2) and impaired IL-2 production, which collectively contribute to immune dysregulation and subsequent podocyte injury [4]. Recent advances in understanding MCD pathophysiology have expanded beyond the traditional T-cell dysfunction hypothesis, with the identification of novel pathogenic factors such as anti-nephrin antibodies opening new research directions [5].

Randomized controlled trials (RCTs) have established the current treatment paradigm for MCD. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [6], corticosteroids remain the first-line therapy, with adult patients receiving prednisone

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(0.8-1 mg/kg/day) for at least 4 weeks. However, the high relapse rate (50%) following treatment reduction necessitates additional immunosuppressive therapy [7]. While calcineurin inhibitors (CNI), particularly tacrolimus, have demonstrated comparable efficacy to steroids in RCTs, with the advantage of reducing steroid-related metabolic complications, concerns about long-term nephrotoxicity persist [8–10] (supplementary Table 1). Other second-line agents, including cyclophosphamide (CTX) and mycophenolate mofetil (MMF), have shown effectiveness but their long-term use is similarly limited by serious side effects.

Rituximab (RTX), a chimeric monoclonal antibody targeting CD20, used in lymphoma and autoimmune diseases [11–13], has emerged as a promising alternative. Its therapeutic potential in MCD stems from triple mechanisms: anti-nephrin antibody-mediated mechanisms, T-cell-mediated mechanisms and direct podocyte protection effects.

This comprehensive review evaluates the emerging role of RTX in adult MCD treatment. Based on a systematic literature search in PubMed (from inception to January 2025) and thorough cross-referencing of relevant publications, we critically analyze six key aspects: (1) mechanistic basis of RTX in MCD treatment; (2) the use of RTX in patients with new-onset MCD; (3) the role of RTX in steroid-dependent or frequently relapsing MCD; (4) RTX-based maintenance therapy; (5) safety profile and adverse events of RTX treatment; (6) future research directions and clinical applications. Ouranalysis seeks to provide evidence-based insights for clinical decision-making while identifying key areas for future investigation.

Mechanistic basis of RTX in MCD treatment

Current evidence suggests that RTX's therapeutic efficacy in MCD may involve multiple potential mechanisms. While the complete picture remains to be fully elucidated, three main mechanisms have been proposed and investigated: anti-nephrin antibody-mediated effects, T-cell-mediated mechanisms, and direct podocyte protection effects.

Anti-nephrin Antibody-mediated mechanisms

Recent advances in MCD pathogenesis have identified anti-nephrin antibodies as crucial pathogenic factors [5]. These antibodies target nephrin, a key protein maintaining podocyte slit diaphragm integrity, with studies revealing their presence in 44% of adult MCD patients and up to 69% in untreated active cases [14]. The pathogenic mechanism of anti-nephrin antibodies involves a cascade of events [15]: (1) antibody binding to nephrin at the slit diaphragm between podocytes, (2) nephrin phosphorylation at Y1191 (corresponding to Y1176 in human nephrin), (3) cytoskeletal reorganization, (4) enhanced nephrin endocytosis, and (5) slit diaphragm disruption, ultimately leading to foot process effacement and proteinuria [5, 14]. This rapid and reversible process explains both the abrupt onset of proteinuria and the quick response to treatment in MCD patients. The enhanced endocytosis mechanism may account for the absence of detectable IgG and electron-dense deposits in MCD patients' biopsies.

The clinical significance of anti-nephrin autoantibodies extends beyond diagnosis, with studies showing correlation between antibody levels and disease severity [5]. Recent investigations have detected IgG antibodies bound to the slit diaphragm in renal biopsy specimens, with co-localization rates of 77.8% of IgG with nephrin in MCD patients [16]. In a case of steroid-dependent MCD that progressed to end-stage kidney disease, high levels of pre-transplant anti-nephrin antibodies were associated with massive post-transplant proteinuria recurrence. After treatment with plasmapheresis and RTX, the patient achieved sustained remission concurrent with the disappearance of these autoantibodies. This case suggests that monitoring anti-nephrin autoantibodies might help identify patients at high risk for post-transplant recurrence, and that plasmapheresis combined with RTX could be an effective therapeutic strategy for such cases [5]. Notably, emerging evidence suggests that RTX may be particularly effective in anti-nephrin antibody-positive cases. In documented cases of anti-nephrin-associated podocytopathy, RTX treatment achieved both immunological remission (through depletion of anti-nephrin antibodies) and clinical remission [14]. RTX effectively reduces these pathogenic antibodies through B-cell depletion, achieved via complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and direct apoptosis induction [16–19].

T-cell-mediated mechanisms

RTX significantly influences T-cell subset distributions [20–22], correcting imbalances in frequently relapsing nephrotic syndrome (FRNS) patients [4]. Studies have demonstrated selective reductions in specific T-cell subsets, particularly affecting CD4 + CD45RO + CXCR5 + cells, INKT cells, and DN-TCR Va24T cells, while maintaining overall T-cell frequencies [4]. This selective modulation suggests RTX's role in restoring T-cell homeostasis, which is crucial for disease remission.

Direct podocyte protection effects

Beyond its immunological effects, RTX directly protects podocytes through multiple pathways: (1) SMPDL-3b-mediated stabilization: RTX binds to SMPDL-3b protein on podocytes, preventing cytoskeletal disruption

Table 1 Overview of studies on different RTX regimens in patients with new-onset and steroid-dependent / frequently relapsing MCD

Author	Study Design	Sample Size	RTX Regimen	CR	Relapse Rate
New-onset MCD					
Fenoglio [23]	Retrospective	6	375 mg/m^2/week × 4 doses	83.30%	0%
Guan [24]	Retrospective	9	375 mg/m^2 × 1–2 doses or 1 g × 2 doses, at d1 and d15	55.60%	11.10%
Xu [25]	Single-center observational	9	1 g × 2 doses, at d1 and d15	88.90%	11.10%
Li [26]	Single-center prospective	74 (20 vs. 28 vs. 26)	Group 1: RTX 1 g × 2 doses, at d1 and 15 Group 2: RTX 1 g at d1 + half-dose pred (0.5 mg/kg/d) Group 3: High-dose pred (1 mg/kg/d)	Group 1: 50% Group 2: 96.4% Group 3: 96.2%	/
Steroid-dependent / frequently relapsing MCD					
Takei [32]	Retrospective	25	375 mg/m^2 at baseline and 6 months	/	16% (12 months) 100% (baseline)
Zhang [33]	Retrospective	33 (Relapse group: 22 Prevention group: 11)	Relapse group: 200 mg/week × 4 doses, then following by 200 mg × 1 every 6 months Prevention group: 200 mg × 1 every 6 months	Relapse group: 86.36% Prevention group: 100%	Relapse group: - Prevention group: 0%
Hansriviji [34]	Systematic review and meta-analysis	221 (MCD: 170 vs. FSGS:51)	Variable	MCD: 74.7% FSGS: 42.9%	MCD: 35.9% FSGS: 47.3%
Xue [35]	Systematic review and meta-analysis	382 (21studies) (MCD/FSGS)	Variable: 375 mg/m^2 × 4 (1-week or 6-month interval) or 1 g × 2 most common (2-week or 6-month interval)	Overall: 84.2% MCD: 91.6% FSGS: 43%	Overall: 27.4% MCD: 27.6% FSGS: 29.8%
Yimamu -yushan [36]	Prospective single-center cohort	60 (MCD: 45 FSGS:15) (SDNS/FRNS: 51 SRNS:9)	RTX 375 mg/m^2/week × 4 doses	Overall: 80% SDNS/FRNS: 88.24% SRNS: 33.33%	Overall: 30.76%
Liu [37]	Retrospective	24	RTX 375 mg/m^2 × 3 doses, 3 weeks interval	91.67%	13.64%
Ma [38]	Multicenter retrospective	48 (MCD: 15 FSGS: 5 MN: 26 MPGN:2)	RTX 375 mg/m^2/ week × 4 doses or RTX 1 g × 2 doses, at d1 and d15	Overall: 66.7% MCD/FSGS: 85% MN: 46.2%	Overall: 6.3% MCD/FSGS: 10% MN: 3.8%
Munyentwali [39]	Retrospective	17	RTX 375 mg/m^2 weekly ×1–4 doses (n = 15); RTX 1 g × 2 doses, at d1 and d15 (n = 2)	65% sustained remission	35%
Guitard [40]	Multicenter retrospective	41	RTX: 1 g × 2 doses, at d1 and d15 or 375 mg/m^2/week × 4 doses	61%	56% at median 18months
Ruggenenti [41]	Academic multicenter off -on trial	30 (MCD/MesGN: 22 FSGS: 8) (children: 10 adults:20)	375 mg/m^2 × 1–2 doses (n = 28 one dose; n = 2 two doses)	/	children:70% adults:40% MCD/MesGN:54.5% FSGS:37.5%
DaSilva [42]	Multicenter retrospective	50 (RTX:28 No RTX: 22) (MCD/MesGN: 43 FSGS: 7)	RTX: 375 mg/m^2 per dose for 1–4 infusions Control: Immunosuppressants without RTX	RTX: 82% Control: 64%	RTX: 29%

Table 1 (continued)

Author	Study Design	Sample Size	RTX Regimen	CR	Relapse Rate
Heybeli [43]	Retrospective	RTX:13 Others:54 (second-line therapy)	RTX: 1 g × 2 doses, at d1 and d15	RTX: 84.6% Others: 83.3%	RTX: 46.2% others:77.8%
Lan [44]	Multicenter retrospective	81 (MCD: 67 FSGS: 14)	RTX 375 mg/m^2 × 2 doses, 2 weeks interval (monitor CD19 + B cells. If not depleted (< 5/μL), give additional 375 mg/m^2 × 2 doses, 2 weeks interval until depletion.)	/	33.3% (12months) 54.3% (24months)
Lin [49]	Retrospective	70 (MCD: 49 FSGS: 21) Consolidation: 22 Non-consolidation: 20	RTX 375 mg/m^2/week × 4 doses. Additional RTX 375 mg/m^2 ×1–2 doses No additional RTX	/	Relapse-free Rate: (24months) Consolidation: 86.36% Non-consolidation: 25%
Osterholt [50]	Multicenter registry-based retrospective	13 (MCD: 10 FSGS:3)	375 mg/m^2/ week × 4 (median 2000 mg per cycle), then, only administering RTX at disease relapse	72% (6 months)	92% (1cycle) 54% (2cycles) 57% (3cycles) 50% (4cycles) 83% (5-8cycles)

Abbreviations RTX, rituximab; CR, complete remission; SDNS/FRNS, steroid-dependent or frequently relapsing nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; MCD, Minimal Change Disease; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy; MPGN, membranoproliferative glomerulonephritis; MesGN, mesangial glomerulonephritis

[14, 19]. (2) IL-4 signaling modulation: RTX modulates IL-4-dependent pathways, affecting podocyte function and survival [22]. (3) Direct cytoskeletal effects: RTX influences podocyte cytoskeleton organization independent of its immunological functions. (4) The reduction of Th17 cells and cytokines: RTX may protect podocytes by reducing Th17 cells and cytokines, directly decreasing IL-17-induced apoptosis and indirectly suppressing inflammatory responses [22]. (5) Additional mechanisms: RTX may affect other signaling pathways involved in podocyte homeostasis, including calcium signaling and oxidative stress responses.

These multiple mechanisms might work synergistically to achieve therapeutic efficacy. While the individual pathways demonstrate promising potential, significant research gaps remain. Notably, comparative studies of RTX efficacy between anti-nephrin antibody-positive and negative patients are currently lacking, representing a critical knowledge gap that could help optimize patient selection and treatment strategies.

The use of RTX in patients with New-onset MCD (Table 1)

While the KDIGO guidelines establish corticosteroids as the front-line therapy for new-onset MCD, they recommend CTX, CNI, or MMF for patients with glucocorticoid contraindications (e.g., severe hyperglycemia, preexisting osteoporosis, glucocorticoid-induced psychosis) [6]. Although RTX traditionally serves as a second-line option for steroid-dependent or relapsing cases, emerging evidence suggests its potential value in early intervention.

Current evidence for RTX in new-onset MCD primarily derives from small, single-center case series studies. In a pioneering study, Fenoglio et al. administered RTX (375 mg/m^2/week × 4) to six treatment-naïve patients, achieving complete remission (CR) in five cases and partial remission (PR) in one case within 6 months. Notably, all patients maintained clinical remission throughout the median follow-up of 21.5 months (8–36 months) after a single anti-CD20 treatment course [23]. More recently, Guan et al. reported outcomes from nine patients treated with RTX (375 mg/m^2 × 1–2 times or 1 g × 2 times), with five achieving CR after a median of 24 days (12–48 days), two achieving PR and only one experiencing relapse [24]. Complementing these findings, our center's experience with nine new-onset patients receiving RTX (1 g/2 weeks × 2) demonstrated CR in eight patients, with five responding within one month. During the 19.84-month median follow-up, only one patient relapsed but achieved subsequent CR with an additional 1 g RTX dose [25].

These collective findings suggest RTX's efficacy in inducing remission in new-onset MCD, particularly benefiting patients at high risk for corticosteroid-related

complications [2]. However, some evidence indicates that RTX's initial induction efficacy may not equal that of glucocorticoids, possibly due to suboptimal dosing strategies [24]. A recent study by Li et al. compared RTX monotherapy with combination therapy and high-dose glucocorticoid regimens in adult MCD treatment. RTX monotherapy demonstrated a significantly lower complete remission rate of 50% at 12 months, compared to 96.4% for combination therapy and 96.2% for high-dose glucocorticoid groups. These findings suggest that while RTX alone may not be sufficiently effective as initial monotherapy, a combination strategy of half-dose prednisolone with RTX appears non-inferior to traditional high-dose glucocorticoid protocols, offering potential advantages in treatment approach [26]. Nevertheless, early RTX intervention shows promise in reducing relapse rates and minimizing cumulative exposure and associated complications compared to conventional approaches.

It is important to acknowledge that these findings are primarily based on small-scale, retrospective studies, which limits the strength of current evidence. To definitively establish RTX's role in new-onset MCD treatment, well-designed multicenter randomized controlled trials are urgently needed. Such collaborative studies would serve multiple purposes: providing robust evidence for RTX's efficacy, standardizing treatment protocols, and identifying optimal patient selection criteria.

The role of RTX in Steroid-Dependent or frequently relapsing MCD (Table 1)

While glucocorticoids remain the first-line therapy for MCD (0.8-1 mg/kg/day prednisone daily for 4–6 weeks), adult patients show distinct treatment challenges. Approximately 25% develop frequent relapses and 30% become steroid-dependent among initial responders [27]. Although CTX has traditionally served as the preferred second-line agent for steroid-dependent or frequently relapsing nephrotic syndrome (SDNS/FRNS) [6], concerns about cumulative toxicity from long-term exposure to steroids and immunosuppressants, including infections, diabetes, osteoporosis, and obesity [28], have prompted exploration of alternative strategies.

Current KDIGO guidelines recommend RTX as an alternative to CTX for patients with SDNS/FRNS [6], and clinical practice increasingly favors RTX over CTX in these cases [29]. While RTX is typically administered in combination with corticosteroids, optimal dosing protocols remain under investigation. Standard regimens include either two doses (1 g each, two weeks apart) or four doses (375 mg/m^2 weekly). Recent evidence suggests that reduced dosing may be effective [30–33]. Takei et al. demonstrated the efficacy of a single dose of RTX 375 mg/m^2 at baseline and six months [32], while Zhang et al. reported success with a low-dose protocol (200 mg/week × 4, followed by 200 mg every 6 months) [33].

RTX has shown significant advantages over conventional immunosuppressive agents in SDNS/FRNS MCD management. Hansrivijit et al. reported that RTX treatment for MCD achieved a total remission (TR) rate of 80.3%, with CR in 74.7% and PR in 5.6% of patients. During a mean follow-up of 27.6 months, the relapse rate was 35.9%, notably in a population predominantly comprising steroid-resistant, frequently-relapsing, or steroid-dependent patients [34]. Similarly, a meta-analysis revealed that RTX achieved a CR rate of 91.6% in adults with SDNS/FRNS of MCD, with a relapse rate of 27.6% during follow-up [35]. Notably, Yimamuyushan et al. observed that the combination therapy of RTX and low-dose glucocorticoids achieved significantly higher complete remission rates in SDNS/FRNS compared to steroid-resistant nephrotic syndrome (SRNS) cases (88.24% vs. 33.33%, $p < 0.01$) [36]. Multiple studies document its efficacy in achieving CR within weeks to months post-administration [32, 36–38]. Takei et al. reported that patients achieved CR within one month after RTX treatment, with 84% maintaining CR during the 12-month follow-up period [32]. Research consistently demonstrates combination therapy with RTX achieves comparable or even higher remission rates compared to conventional treatment, along with significant reductions in relapse rates and required doses of steroids and immunosuppressants [32, 37, 39–44]. In a comparative analysis of four second-line therapeutic options for adult SDNS/FRNS, Heybeli and colleagues demonstrated that RTX exhibited superior efficacy compared to MMF, CNI, and CTX. The RTX cohort achieved significantly longer median relapse-free survival (66 vs. 28 months), higher rates of steroid discontinuation (92.3% vs. 62.5–83.3%), and superior complete drug withdrawal rate (84.6% vs. 16.7–37.5%) [43]. Notably, many patients who discontinued steroids or immunosuppressive agents maintained long-term remission during follow-up [32, 37, 39, 41], establishing RTX as an effective option that not only prevents relapse but also reduces dependence on conventional immunosuppressive therapy.

In addition, recent evidence suggests that RTX may be particularly effective in anti-nephrin antibody-positive cases. In three documented cases of anti-nephrin-associated podocytopathy, RTX treatment led to both immunological remission (depletion of anti-nephrin antibodies) and clinical remission, suggesting that RTX-induced remission may be achieved through autoantibody depletion in addition to its effects on T-cells. While these findings are based on a limited number of cases, they might provide important mechanistic insights into RTX's therapeutic efficacy [14].

RTX-based maintenance therapy in MCD

The role of RTX in maintaining long-term remission has evolved significantly since its first successful application in MCD patients with SDNS in 2006 [45]. Accumulating evidence supports its efficacy in sustaining disease remission, with comparative studies demonstrating superior outcomes compared to conventional treatments. In a landmark study, Heybeli et al. reported significantly extended remission duration with RTX versus alternative therapies (median: 66 vs. 28 months, $p < 0.001$) [43], establishing its potential as a maintenance agent.

Optimal dosing strategies

The relationship between dosing protocols and remission duration has emerged as a critical consideration. Studies indicate that initial dosing frequency significantly influences outcomes, with three to four RTX infusions (375 mg/m²) achieving substantially longer remission compared to one or two doses (23.3 ± 18.7 vs. 10.3 ± 3.5 months) [46]. Dose-optimization research has revealed that lower doses (50 mg/m²) may achieve comparable B-cell suppression and antibody response modulation to standard dosing (375 mg/m²) [47]. However, in patients with heavy proteinuria, enhanced RTX dosing may be necessary due to urinary loss of the drug, potentially affecting its pharmacokinetics and therapeutic efficacy [48]. This consideration is particularly relevant in the initial treatment phase when proteinuria is most severe, suggesting that dose adjustments based on proteinuria severity might be warranted.

Previous studies have demonstrated that consolidation therapy with rituximab at 6 months post-initial course significantly improves 24-month relapse-free survival compared to non-consolidation groups (86.36% vs. 25%) [49]. The Cox proportional-hazards model revealed a substantially lower relapse risk in the consolidation group (odds ratio 20.9, $p < 0.001$), underscoring the critical necessity of RTX maintenance therapy [49]. For maintenance therapy, both standard (375 mg/m²) and reduced (200 mg) semi-annual dosing have demonstrated effectiveness in sustaining remission without concurrent immunosuppression [19, 20]. Notably, Osterholt et al. administered RTX only upon disease relapse, which not only significantly reduced RTX exposure (43 cycles vs. 219 cycles) but also maintained comparable therapeutic effectiveness, with no evidence of developing resistance [50]. The median relapse-free survival increased from 4.5 months with previous regimens to 21 months after RTX initiation ($p < 0.001$) offering flexible treatment options based on individual patient responses [50].

Monitoring parameters and disease activity

Traditional monitoring through B-lymphocyte quantification presents a complex relationship with disease activity. While B-cell recovery typically begins around 6 months post-RTX and reaches normal levels by 12 months, the correlation with relapse risk remains inconsistent. Most studies link CD20-B cell recovery with relapse [7, 39, 45, 51]. However, several observations challenge the direct B-cell-relapse paradigm: (1) Proteinuria recurrence despite complete B-cell depletion; (2) Disease relapses in patients with undetectable CD19 + B-cells [40, 52]; (3) Sustained remission despite B-cell recovery [31, 39, 40, 53].

These findings suggest the involvement of B-cell-independent pathogenic mechanisms and highlight the limitations of B-cell quantification as a sole monitoring parameter. The recent identification of anti-nephrin autoantibodies offers a promising alternative biomarker for disease monitoring. Implementation of systematic anti-nephrin autoantibody monitoring may provide more precise correlation with clinical manifestations and enable optimized therapeutic decision-making, particularly in maintenance therapy adjustment.

Safety profile and adverse events of RTX treatment

The safety profile of RTX in MCD patients has been documented through both MCD-specific studies and extrapolated data from larger studies in other autoimmune conditions. In MCD-specific studies, the most commonly reported adverse events were mild infusion reactions (fever, chills, and rash) [35], which could be effectively managed through reduced infusion rates and prophylactic administration of acetaminophen, corticosteroids, and antihistamines. However, in rare cases, life-threatening complications such as disseminated intravascular coagulation-like reactions have been reported, characterized by severe thrombocytopenia and coagulopathy, which may limit its use in certain patients [54].

More severe complications have been primarily documented in studies of other conditions, though these risks remain relevant to MCD patients due to similar immunosuppressive mechanisms. A significant concern is RTX's B-cell-depleting effect, which may lead to hypogammaglobulinemia and increased infection susceptibility. While overall infection rates in MCD patients remain relatively low [35], severe infections can occur, with Pneumocystis jirovecii pneumonia (PJP) being particularly concerning in immunocompromised patients. Data from larger autoimmune cohorts have identified hepatitis B virus (HBV) reactivation as another significant risk, with reactivation rates of 30–60% in HBsAg-positive patients and > 10% in HBcAb-positive/HBsAg-negative patients [55]. Current guidelines mandate HBsAg and HBcAb screening before RTX initiation. For HBsAg-positive patients, prophylaxis with potent antivirals (entecavir, tenofovir disoproxil fumarate [TDF], or tenofovir alafenamide [TAF]) is recommended. For HBsAg-negative/

anti-HBc positive patients, lamivudine is recommended, while entecavir, tenofovir, or TAF should be considered for extended immunosuppression. Prophylaxis should continue for at least 18 months after rituximab discontinuation with 12 months additional monitoring, and can be stopped only if the underlying disease is in remission [56]. Additionally, active tuberculosis must be treated before RTX initiation, as RTX therapy can exacerbate tuberculosis through multiple mechanisms including B-cell depletion, altered T-cell function, and potential neutropenia, all of which contribute to increased immunosuppression.

Comparative studies between RTX and corticosteroid therapy in MCD patients suggest that RTX may offer a more favorable safety profile, especially given the significantly increased rates of infection and steroid-induced diabetes in the corticosteroid group [26]. However, continued vigilance and long-term safety monitoring remain essential, particularly given the relatively recent adoption of RTX in MCD treatment.

Future research directions and clinical applications

Despite accumulating evidence supporting RTX efficacy in MCD, current literature remains predominantly limited to retrospective studies with small sample sizes and inadequate controls. Large-scale, prospective, controlled trials are essential to definitively establish RTX's therapeutic efficacy, optimal dosing strategies, and long-term outcomes in adult MCD. Several important clinical trials are currently ongoing, including the RIFIREINS trial in France and the TURING trial in the UK. These trials are expected to provide valuable evidence on optimal RTX timing and its role in preventing relapses. Key research priorities encompass: (1) determination of optimal initial and maintenance dosing protocols; (2) identification of patient-specific response factors; (3) comparative evaluation against conventional therapies; and (4) comprehensive assessment of long-term safety profiles across diverse populations.

RTX demonstrates promising therapeutic potential across multiple clinical scenarios. In new-onset adult MCD, emerging evidence supports its consideration as first-line therapy, particularly for patients with poor glucocorticoid tolerance. For SDNS/FRNS patients, RTX effectively reduces disease recurrence following glucocorticoid-induced remission while facilitating steroid discontinuation. Preliminary data suggest that combination strategies incorporating RTX with conventional immunosuppressants may optimize therapeutic outcomes while minimizing adverse events, though standardized protocols require further validation.

The identification of anti-nephrin autoantibodies represents a significant advancement in understanding MCD pathogenesis, offering novel applications in disease diagnosis, treatment monitoring, and prognosis evaluation. This discovery provides opportunities for developing targeted therapeutic strategies and personalized treatment algorithms. While RTX is now incorporated into international guidelines for adult MCD management, the relationship between anti-nephrin antibody status and treatment response remains unclear. Currently, evidence comparing RTX efficacy between antibody-positive and negative patients is limited, representing a critical knowledge gap in the field. Future research should prioritize investigating whether antibody status could predict RTX response, as such findings would be instrumental in developing personalized treatment strategies. The continued investigation of anti-nephrin autoantibodies, coupled with rigorous clinical validation, may fundamentally transform current therapeutic paradigms, enabling more precise and effective interventions.

Conclusions

Based on the comprehensive review, RTX has emerged as a promising therapeutic approach for adult MCD, offering a nuanced alternative to traditional glucocorticoid therapy. Its efficacy stems from multiple mechanisms, including anti-nephrin antibody depletion, T-cell subset modulation, and direct podocyte protection. While current guidelines still recommend glucocorticoids as first-line treatment, RTX demonstrates significant potential, particularly for steroid-dependent or frequently relapsing patients, with studies showing encouraging complete remission rates and substantially reduced relapse rates. The discovery of anti-nephrin antibodies has provided crucial insights into MCD pathogenesis, offering new opportunities for personalized treatment strategies. Despite its promising results, the field requires large-scale prospective controlled trials to definitively establish optimal dosing protocols, long-term safety profiles, and precise patient selection criteria. The ongoing research suggests that RTX is poised to play an increasingly important role in adult MCD management, potentially transforming current therapeutic paradigms by offering more precise, mechanism-based interventions.

Abbreviations

MCD	Minimal Change Disease
RCTs	Randomized Controlled Trials
RTX	Rituximab
CNI	Calcineurin Inhibitors
CTX	Cyclophosphamide
MMF	Mycophenolate Mofetil
KDIGO	Kidney Disease: Improving Global Outcomes
CR	Complete Remission
PR	Partial Remission
SDNS/FRNS	Steroid-Dependent or Frequently Relapsing Nephrotic Syndrome
TR	Total Remission
SRNS	Steroid-Resistant Nephrotic Syndrome
PJP	Pneumocystis Jirovecii Pneumonia
HBV	Hepatitis B Virus

TDF	Tenofovir Disoproxil Fumarate
TAF	Tenofovir Alafenamide

Supplementary Information

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Supplementary Material 1

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Author contributions
An-ni Zhong wrote the initial manuscript. Yi Yu, Tao Cao, and Qi-jun Wan contributed to manuscript revision and literature review. Ri-cong Xu was responsible for reviewing and editing the paper with substantial revisions and supervised the entire project.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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