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Review Article

Mechanisms and Clinical Research Progress of Rituximab in the Treatment of Adult Minimal Change Disease

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Abstract

Introduction: Minimal change disease (MCD) is a common subtype of primary nephrotic syndrome in adults. The pathogenesis of MCD is still not well understood, but some studies suggest that MCD is a T cell-mediated disease related to podocyte dysfunction. Previous research has also indicated the crucial role of B cells in the pathogenesis of MCD. Rituximab (RTX) is a recombinant chimeric mouse/human antibody targeting CD20 antigen. In recent years, RTX has been increasingly used in adult MCD patients.

Methodology: We searched the PubMed database using the keywords "Minimal change disease", "Nephrotic syndrome", and "Rituximab" and obtained a total of 140 articles. We will now provide a literature review based on these 140 articles, according to our research topic.

Discussion: This article provides an overview of the mechanisms and clinical research progress of RTX in the treatment of adult MCD. We have also discussed the current treatment methods for MCD, exploring the potential of using RTX as a first-line therapy for refractory adult MCD.

Conclusion: MCD is a common pathological type of nephrotic syndrome, and the exact mechanisms are still not fully understood. Although RTX as a treatment of adult MCD has shown promising clinical results in patients with refractory adult MCD, the safety and efficacy of RTX still lack high-quality clinical evidence. Further research is needed to explore the pathogenesis of MCD and the RTX treatment for MCD.

More Information

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Introduction

Minimal change disease (MCD) is a common pathological type of nephrotic syndrome, accounting for approximately 90% of idiopathic nephrotic syndrome in children [1]. In adults, MCD represents about 10% - 15% of patients with idiopathic nephrotic syndrome [2]. The main clinical manifestations of MCD include hypoalbuminemia, proteinuria, edema, and hyperlipidemia. The pathological characteristics are as follows: no glomerular lesions under light microscopy (or only mild mesangial proliferation); diffuse fusion of podocyte foot processes observed by electron microscopy, but no electron-dense deposits; negative immunofluorescence (or only low-intensity C3 and IgM deposits) [3,4]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [5], the traditional treatment approach for MCD typically involves the administration of corticosteroids, specifically oral prednisone. Prednisone is commonly used as the initial therapy due to its anti-inflammatory and immunosuppressive properties. The standard treatment protocol for MCD consists of an initial high-dose phase [5], followed by a gradual tapering of the steroid dosage over several weeks. The high-dose phase aims to induce remission and reduce proteinuria. If there is a positive response to the initial treatment, a maintenance phase with a lower dose of prednisone is initiated to sustain remission and prevent relapse. In cases where MCD does not respond adequately to corticosteroids or if there is frequent relapse, additional therapies may be considered. These alternative treatments may include immunosuppressive agents such as cyclophosphamide, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), or mycophenolate mofetil [6]. These medications target the immune system and help control the abnormal immune response that contributes to MCD.

Rituximab (RTX) is a recombinant chimeric mouse/human antibody targeting the CD20 antigen, which is a hydrophobic transmembrane protein present in normal

and mature B lymphocytes [7]. In 2002, there was the first report suggesting the use of RTX in patients with primary membranous nephropathy (pMN) [8]. Since then, RTX has gradually become the preferred treatment for pMN due to its demonstrated high safety and effectiveness. Several non-randomized studies have shown remission rates ranging from 57% to 89% in pMN patients treated with rituximab [8-11]. In recent years, RTX has also been recommended for the treatment of MCD. A recent observational study has shown that rituximab treatment can reduce the disease relapse rate in adult patients with MCD [12]. However, there is currently more research on RTX in children with MCD, while there is limited research on adults with MCD. This review aims to explore the potential pathogenic mechanisms of MCD and the mechanisms and clinical applications of RTX in treating MCD.

Mechanisms of RTX in the treatment of MCD

I. **Pathogenesis of minimal change disease:** The exact pathogenic mechanisms of MCD are currently unclear, but many studies suggest that podocyte injury, with T cell dysfunction as an important pathogenic factor, plays a major role in this disease. As early as 1972, Shalhoub, et al. [13] proposed the hypothesis that MCD is an immune-mediated disease, in which a lymphokine produced during T cell proliferation has a toxic effect on the glomerular basement membrane, leading to podocyte injury and massive proteinuria [14]. This hypothesis was based on the following four aspects: 1) the remission of MCD after measles infection suggests a response to cell-mediated immune suppression caused by measles; 2) MCD can occur in Hodgkin's disease; 3) immunosuppressive therapy may be effective in treating MCD; 4) pathological examination shows no immunoglobulin or complement deposits in the glomerulus, which distinguishes it from other glomerular diseases [5,15]. Studies have shown that the supernatant of T cell hybridoma cell lines produced by MCD patients can induce the disappearance of rat kidney podocyte foot processes and the production of proteinuria [16], providing evidence for the aforementioned hypothesis. A multicenter randomized controlled trial conducted by Boumediene, et al. [17] also confirmed the changes in T cell subsets observed during the course of MCD in patients.

Due to the increasing clinical use of B cell-targeted drugs such as rituximab (RTX), more and more research has begun to focus on the role of B cells in minimal change disease (MCD). A multicenter randomized controlled trial [18] showed that proteinuria in some patients improved after B cell depletion. The trial also demonstrated the feasibility of reducing the dosage of immunosuppressants in the treatment process of up to 85% of patients, and some patients were even able to discontinue one or more immunosuppressants. No relapse was observed during the period of B cell depletion, and there was no significant difference in adverse events between the treatment groups. However, there are also studies that do not support the involvement of B cells in the occurrence and development of MCD. Firstly, according to the definition of MCD, there are few or no immunoglobulin deposits in renal biopsies of MCD. In vitro, it has been demonstrated that RTX directly binds to podocyte SMPDL3b, and its anti-proteinuria effect may be unrelated to B cell depletion [19]. In addition, some patients are able to maintain long-term remission even after B cell reconstitution following RTX infusion [20]. Regarding this aspect, previous studies have indicated that in children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome, the reconstitution of memory B cells after RTX-induced B cell depletion can predict relapse [21,22]. Targeting B cells may affect the co-stimulatory pathways involved in T cell activation, which is likely one of the mechanisms underlying the efficacy of CD20 depletion agents [23].

II. **Possible mechanisms of rituximab treatment in minimal change disease:** Recently, RTX has been increasingly used in adult MCD patients, especially in the treatment of refractory cases. Upon binding, RTX triggers a cytotoxic immune response against CD20-positive cells. Several possible mechanisms of RTX treatment in minimal change disease (MCD) have been suggested [24], including B cell depletion, indirect/direct effects on T cells, and direct effects on podocytes.

1. B Cell Depletion by RTX in the Treatment of MCD

(1) Antibody-dependent cell-mediated cytotoxicity (ADCC): RTX binds to the CD20 receptor on B lymphocytes through its Fab region while exposing its Fc region to effector cells such as natural killer cells, macrophages, and neutrophils [25,26].

(2) Complement-dependent cytotoxicity (CDC): Similar to ADCC, B lymphocytes form complexes with RTX, activating the complement cascade, leading to the formation of membrane attack complexes and subsequent cell lysis.

(3) Direct effects on abnormal B lymphocytes: The mechanisms behind the direct effects of RTX on abnormal B lymphocytes are not fully understood. Once complexes are formed, the affected cells may undergo apoptosis, proliferation inhibition, and cell cycle changes [27]. B cell depletion may reduce the production of aberrant self-reactive antibodies, explaining its presumed efficacy in various autoimmune renal diseases.

2. Effects on T Lymphocytes

(1) B cell depletion may benefit T cell-mediated diseases. This view is based on the role of B cells in providing co-stimulatory signals for T cell activation and regulation.

B cells regulate T cell responses through co-stimulatory molecules [28,29]. The interaction between CD40 on B cells and CD40L (CD154) on T cells, as well as the interaction between CD80 (B7-1) or CD86 (B7-2) on antigen-presenting cells and CD28 on T cells, induces co-stimulation. In patients with lupus nephritis (systemic lupus erythematosus, SLE), RTX treatment has been associated with a significant reduction in CD40L mRNA, downregulation of CD40L on Th cells, and downregulation of CD40 and CD80 on residual B cells. These changes were correlated with reduced T-cell activation and certain favorable clinical responses [30]. Thus, it can be inferred that RTX blocks T cell co-stimulatory pathways in MCD, thereby modulating T cell function.

(2) RTX has been shown to regulate Treg cells, and recent studies [30-32] have found that these cells may impact disease relapse in nephrotic syndrome.

Thymus-derived naturally occurring Treg cells are defined by the co-expression of CD4, CD25, and the transcription factor Forkhead box P3 (Foxp3) [33]. Treg cells exert immune suppressive effects through various mechanisms, including the production of inhibitory cytokines, such as IL-10 and TGF-β [34]. The expression of Foxp3 in mature Treg cells is essential for their suppressive function, and loss of Foxp3 expression leads to the production of characteristic cytokines of other Th cell lineages [35]. Maintaining a relative balance between the regulatory T cell and effector T cell lineages seems crucial for immune homeostasis. The loss of Treg cells is associated with autoimmunity and may be related to chronic inflammation [36].

Studies have reported a significant decrease in the number and percentage of peripheral Treg cells (CD4+, CD25+, Foxp3+) during active MCD compared to remission and healthy control groups [37-40]. Treg cells and Treg-associated cytokines (TGF-β1 and IL-10) were decreased during proteinuric periods and returned to normal levels after inducing remission [41]. RTX may increase the number of Treg cells and restore their defective regulatory function in certain autoimmune diseases [42]. However, the exact mechanism by which RTX increases or restores the number and/or function of Treg cells in MCD remains unclear. Additionally, some T cells may express the CD20 receptor, allowing for direct effects of RTX [43].

3. Direct effects on podocytes

Previous research [19] has shown that RTX can bind to sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) on the surface of podocytes, regulating acid sphingomyelinase activity and preventing disruption of the actin cytoskeleton and podocyte apoptosis. However, the mechanism is still uncertain in clinical applications [35].

Clinical studies on the use of RTX in the treatment of adult MCD

Despite the current lack of evidence from randomized controlled trials (RCTs), RTX has been widely utilized in the treatment of corticosteroid-dependent, frequently relapsing, and refractory MCD. Research indicates that RTX therapy for MCD is safe and effective [44].

A retrospective study included 17 patients with corticosteroid-dependent or frequently relapsing MCD who received RTX treatment and were followed up for a mean duration of 26.7 months. During the follow-up period, approximately 65% of the patients did not experience a relapse, with 9 patients successfully discontinuing corticosteroids and other immunosuppressive medications. Among the patients who achieved sustained remission, 64% maintained it for more than 20 months [45]. Subsequent retrospective cohort studies have also reached similar conclusions, highlighting the safety and efficacy of RTX in treating refractory MCD in adults, and its ability to reduce relapse rates and the use of other immunosuppressive agents [17,48,49].

We reviewed the following studies, and the results consistently indicate that the use of RTX for the treatment of adult MCD can yield positive outcomes, with a low incidence of adverse events Table 1.

According to the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and the consensus from the Chinese Society of Nephrology, RTX is recommended for the treatment of adult MCD, particularly for adults with refractory MCD. The recommended treatment regimens include a two-dose regimen (1g per dose, two doses with a 2-week interval), a four-dose regimen (375mg/m2 once weekly for a total of four doses), and a B-cell guided regimen (375mg/m2 single dose, with repeat doses depending on CD19+B cell count after one week). For patients with relapse after induction, the guidelines suggest an intravenous infusion of 375mg/m2 or 1g as a single dose. According to the KDIGO guidelines, RTX treatment for adult MCD not only reduces the frequency of relapses and the use of immunosuppressive agents but also increases the induction remission rate to 65% - 100% [50].

A systematic review and meta-analysis of 11 studies on RTX treatment for adult MCD reported an overall remission rate of 80%, a relapse rate of 36%, and a low incidence of severe adverse events at 0.092 per year, suggesting the safety and efficacy of RTX in treating adult MCD [51]. However, further RCTs are needed to establish the safety, efficacy, and appropriate dosage of RTX treatment for adult MCD, especially as an initial therapy.

Discussion, recommendations and perspectives

MCD is the most common pathological subtype of nephrotic syndrome. The clinical presentation of MCD is characterized by hypoalbuminemia, proteinuria, edema, and hyperlipidemia. Pathologically, MCD is characterized by the absence of glomerular lesions under light microscopy,

Table 1: Therapy procedures for adults [17,44-47].

Research	Patients	Conclusion
2013 Kidney Int	17 patients with corticosteroid-dependent or frequently relapsing MCD	Approximately 65% of the patients did not experience a relapse, with 9 patients successfully discontinuing corticosteroids and other immunosuppressive medications.
2018 J Autoimmun	23 cases of relapsed and refractory MCD patients	Among the 10 patients in the RTX group, 9 of them were able to reduce the use of immunosuppressive drugs and maintain remission, while in the placebo group of 13 patients, relapse occurred at a median of 7.3 weeks.
2017 BioDrugs	50 cases of adult patients with steroid-dependent/frequently relapsing idiopathic nephrotic syndrome	The complete remission rate in the RTX group is 82%, while it is 63% in the control group. The annual relapse rate is significantly reduced after RTX treatment (P<0.001), and the proportion of patients with sustained remission is higher than that of the control group.
2014 Nephrol Dial Transplant	41 cases of adult patients with MCD	The overall remission rate reached 78%. The median follow-up time was 39 months, with 18 patients (56%) experiencing a relapse? Among them, 17 patients achieved clinical remission again after receiving the second course of RTX treatment. Nine patients maintained remission even after B cell recovery, and no serious adverse events occurred.
2021 BMC Nephrol	25 cases of adult patients with MCD	22 patients achieved complete remission, with an average duration of 3.26 months. During the follow-up period, only 3 patients had a single relapse. The average duration of remission maintenance was 11.6 months, and it was 5 months after discontinuing steroids. The last recorded dose of steroids during follow-up was 6.09mg/d, which was significantly lower than the pre-rituximab dose of 28.15mg/d. The relapse rates before and after rituximab were 1.43 and 0.1 respectively. Only four mild adverse events were recorded.

or only mild mesangial proliferation, as well as diffuse fusion of podocyte foot processes observed through electron microscopy without any electron-dense deposits. Immunofluorescence testing usually shows negative results, or at most, low-intensity deposits of C3 and IgM.

The standard treatment for MCD typically involves the use of corticosteroids, particularly oral prednisone. Prednisone is chosen as the initial therapy due to its potent anti-inflammatory and immunosuppressive properties. The treatment protocol for MCD usually consists of an initial high-dose phase, followed by a gradual tapering of the steroid dosage over several weeks. The aim of the high-dose phase is to induce remission and reduce proteinuria. If there is a positive response to the initial treatment, a maintenance phase with a lower dose of prednisone is initiated to sustain remission and prevent relapse. However, in cases where MCD does not respond adequately to corticosteroids or if there is frequent relapse, alternative therapies may be considered. These alternative treatments may include immunosuppressive agents such as cyclophosphamide, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), or mycophenolate mofetil. These medications target the immune system and help control the abnormal immune response that contributes to MCD. In recent years, RTX has also been recommended for the treatment of MCD, and it has been demonstrated that rituximab treatment can significantly reduce the relapse rate in adult patients with MCD. However, while there is ample research on the use of RTX in children with MCD, there is limited research on its application in adults with MCD. Therefore, we need more RCT studies that aim to explore the underlying pathogenic mechanisms of MCD as well as the mechanisms and clinical applications of RTX in the treatment of MCD.

According to the research mentioned above, the use of RTX as a treatment option for adult refractory MCD patients has significant advantages. RTX therapy can reduce the use of steroids and immunosuppressants, thereby reducing the risk of side effects and adverse events caused by these medications. Using RTX as a treatment modality can significantly decrease the relapse rate in adult refractory MCD patients, thus improving the durability of the treatment efficacy. It also improves the patient's quality of life by reducing the dependence on medication and the frequency of relapses. With advances in clinical randomized controlled trials (RCTs) and the understanding of the pathophysiology and immunology mechanisms of MCD, we are optimistic about the prospect of RTX as a first-line treatment for adult refractory MCD. Currently, some clinical studies have demonstrated the effectiveness and safety of RTX in adult refractory MCD patients. In recent years, the progress in studying the pathological and immunological mechanisms of MCD has increased our understanding of the therapeutic mechanisms of RTX in treating this disease. Based on the above information, it is reasonable to predict that RTX is likely to be included in the first-line treatment strategy for adult refractory MCD in the future. However, ensuring its effectiveness and safety in real-world clinical practice still requires more large-scale, multicenter, randomized controlled trials for further validation. Only then can the position of RTX in adult refractory MCD and the optimal application plan be accurately determined.

Conclusion

In conclusion, MCD is a common pathological type of nephrotic syndrome in adults, and the exact mechanisms underlying its development are still not fully understood. The role of T lymphocytes in the pathogenesis of MCD is relatively clear, while the involvement of B lymphocytes in the onset and progression of MCD remains controversial. Although RTX has been recommended in international and domestic guidelines for the treatment of adult MCD and has shown promising clinical results in patients with refractory adult MCD, the safety and efficacy of RTX still lack high-quality clinical evidence. Further research is needed to explore the pathogenesis of MCD and the basic and clinical aspects of RTX treatment for MCD.

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