Anti-CD20 antibody as Initial therapy for adult-onset minimal change disease with nephrotic syndrome:a case series report

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Anti-CD20 antibody as Initial therapy for adult-onset minimal change disease with nephrotic syndrome:a case series report

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Abbreviations : MCD:minimal change disease;NS: nephrotic syndrome; CyC: cyclophosphamide; Cys: cyclosporine; TAC: tacrolimus; RTX: rituximab; OTZ: obinutuzumab; IGT: impaired glucose tolerance; ALB: albumin; TG: tolal cholesterol; TC: triglycerides; WBC: white blood cell;Scr: serum creatinine; PR: partial remission; CR:complete remission; AE:adverse events

Keywords : minimal change disease; CD20; nephrotic syndrome; rituximab; obinutuzumab

Abstract

Minimal change disease (MCD) is one of the most common pathological types of primary nephrotic syndrome. High-dose glucocorticoid therapy is the initial treatment for MCD; however, the long-term use of high-dose glucocorticoids can lead to serious adverse events. Therefore, research into non-hormone-containing regimens is increasing. In recent years, There has been some progress in the use of rituximab for the treatment of refractory, steroid-dependent, or relapsing MCD. However, little research has been conducted on the use of rituximab as the initial treatment option for MCD. This paper reports the results of treating five patients with confirmed MCD using a single-agent anti-CD20 antibody regimen. Our results show that anti-CD20 antibody is effective as a first-line treatment for adult MCD without significant adverse reactions. In addition, we reviewed the currently published literature and found there are two series of case reports of RTX as first-line treatment for MCD in adults. The results of these two series of cases also show that anti-CD20 antibody is effective as a first-line treatment for adult MCD without significant adverse reactions. This regimen provides more options for patients who are unwilling to use hormones or have contraindications for hormone use.

Introduction

Minimal change disease (MCD) is the third most common primary kidney disease (10% to 17%) in adults with idiopathic nephrotic syndrome (NS)[1]. Steroids have been widely used to treat adult-onset MCD since the early 1970s. However, 10% to 30% of adults with MCD fail to respond to corticosteroids[2], 70% to 80% relapse after NS remission[2], 10% to-30% occur frequently relapse, and 15% to 30% become steroid

dependent[3]. Additionally, adverse effects of long-term corticosteroid use remain a significant challenge in clinical practice. Few studies have shown that these alternative regimens, such as cyclophosphamide (CyC), cyclosporine (Cys)[4], tacrolimus (TAC)[5], and low-dose prednisone with mycophenolate (MPA)[6], as first-line treatments for MCD, have no obvious advantages in terms of either efficiency or adverse effects compared with corticosteroids. Therefore, newer treatments for adult MCD should be explored to improve the remission rate and reduce the risk of side effects.

Cell depletion agents include chimeric, human, and humanized monoclonal anti-CD 20 antibodies. Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody first applied to MCD in 2006[7]. Since then, it has been used to treat relapsing NS in children]. A recent study showed that RTX could be used to treat frequently relapsing and glucocorticoid-dependent MCD in adults, leading to a reduction in the frequency of relapse and facilitation of glucocorticoids withdrawal[8, 9]. New human and humanized monoclonal anti-CD20 antibodies offer some advantages based on their stronger effects on CD20 cell subtypes, and have already been administered in hematology and oncology as substitutes for chimeric molecules; however, research on their application in glomerular diseases is limited. Whether anti-CD20 antibody is the best front-induction therapy for MCD remains to be explored. In this article, we retrospectively reviewed the efficacy and safety profile of the anti-CD20 antibody as an initial treatment for five biopsy-proven adult patients with MCD. Furthermore, we analyzed the previous literature on RTX applied to the front MCD to deepen our understanding of this issue.

Case series report

Five adult patients with renal biopsy-proven MCD were enrolled in the study. The patients were initially treated with anti-CD20 antibodies because of their unwillingness to use glucocorticoids or glucocorticoid-related side effects. All patients received at least one course of anti-CD20 (rituximab, RTX, or obinutuzumab, OTZ) antibody treatment (two infusions of 1000 mg every 14 days). Therapeutic effects were assessed by measuring 24-hours urinary protein and serum albumin levels. Complete remission (CR) was defined as 24-hours urinary protein defined as a decrease in 24-hours urinary protein of more than 50% from the baseline.

Case 1

A 74-year-old woman was diagnosed with an MCD in July 2022. She had hypertension for more than 20 years and impaired glucose tolerance (IGT) for one year. The Body Mass Index (BMI) was 24.6 kg/m2. Laboratory analyses revealed a urinary protein level of 4745 mg/day, serum albumin (ALB) level of 26 g/L, serum total cholesterol (TC) level of 8.44 mmol/L, and serum IgG 6.12g/L(Table 1). The patient was initially treated with RTX on August 4th and August 18th 2022. The patient was followed-up for 18 months. She achieved partial remission (PR) with a decreased urinary protein level from 5724 mg/d to 2134 mg/d 1 month after treatment and achieved complete remission (CR) within 3 months. CD19+ cells were monitored during follow-up. Six months after receiving RTX, although CD19+ cells were undetectable, the disease relapsed with increased urinary protein levels from 267 mg/day to 4587 mg/day. She then received RTX (1 g) again and achieved a >50% decrease in urinary protein excretion three months after the second infusion of RTX. At the last follow-up, the urinary protein level was less than 1 g/day, and ALB, serum IgG, and TC levels were normal. The renal function remained stable during the follow-up period (Table 2).

Case 2

A 71-year-old man was diagnosed with MCD in September, 2022. He had urarthritis for more than 10 years. BMI was 22.4 kg/m2. Subsequent laboratory tests showed a urinary protein level of 6541 mg/day, ALB level of 21 g/l, and TC level of 8 mmol/L (Table 1). RTX treatment on September 22 and October 7, 2022. Proteinuria declined in months 1 and 3 to 1678 mg/day (PR) and 178 mg/day (CR), respectively. Peripheral CD19+ cells were undetectable until nine months after RTX treatment. At the 24 months follow, the patient's renal function was stable and CR was maintained (Table 2).

Case 3

An 18-year-old man was diagnosed with MCD in September 2022. The patient had no relevant medical histories. BMI was 21.4 kg/m2. Results from a 24-hours urine protein excretion test detected 23445 mg of protein. TC and ALB were 17.76 mmol/L and 12 g/L, respectively (Table 1). He received OTZ on September 9 and 24, 2022. One month after the start of OTZ treatment, the patient responded with a Stable as 24 hours protein decreased of 96.5% (from 23445 to 832 mg/day). The urinary protein levels were normal by the third month (Table 1). It is worth noting that peripheral CD19+ cells remained depleted by 18 months follow-up (Table 2).

Case 4

A 29-year-old woman was diagnosed with an MCD in September 2021. The patient had no relevant medical histories. BMI was 25.9 kg/m2. Laboratory tests revealed massive proteinuria (15, 651 mg/day), decreased albumin (17 g/L), and elevated cholesterol (7.47 mmol/L), as shown in Table 1. RTX infusion was administered on September 8, 2021, and September 26, 2021. Her urine protein level decreased to 394 mg/day two weeks after the first dose of RTX, and she still received a second dose of RTX according to the initial regimen. Peripheral CD19+ cells recovered nine months after RTX treatment (Table 2). No relapse has been documented for more than three years of follow-up. Fortunately, she has successfully given birth to a healthy child, and the disease remains in remission.

Case 5

A 58-year-old man diagnosed with MCD in August 2021. He had a history of hypertension for more than five years, IGT for one month, and urarthritis for three years. BMI was 26.3kg/m2. Major biological abnormalities were observed in laboratory tests: low ALB (24 g/L), massive proteinuria (7924 mg/L), and elevated cholesterol (8.38 mmol/L). Immuno-electrophoresis revealed IgM $\varkappa$,IgM with 2.59 g/L (reference range: 0.46-3.04), IgG with 4.28 g/L (reference range: 7.51-15.6), and IgA with 3.38 g/L (reference range: 0.82–4.53) (Table 1). Bone marrow aspirate, immunophenotypic analysis of bone marrow cells, and kappa/lambda-free light chains (FLCs) showed normal results, and multiple myeloma diagnoses were discarded. The patient was treated with RTX on August 11th and 27, 2021. Proteinuria decreased at a slower rate in this patient than in the previous four patients. The time to achieve PR and CR was 3 and 12 months, respectively (Table 2). Peripheral CD19+ cells were detected six months after RTX infusion. RTX offers sustained and long-term remission (> three years).

Overall, only Patient 1 received repeated RTX therapy and eventually achieved PR. The other four patients received only one course of RTX or OTZ treatment, maintained a sustained CR, and were relapse free. All five patients were administered antiallergic symptomatic treatments before RTX or OTZ infusion to avoid infusion-related symptoms. There were no infusion-related hematological reactions or any other serious adverse events at the end of follow-up.

Literature reviews

Research on the use of anti-CD20 antibodies as first-line treatment for MCD is limited. We found two series of case reports of RTX as first-line treatment for MCD in adults. In one case series report, eight patients were treated with a single dose of RTX (375 mg/ m2) and one patient with RTX (1 g twice). Five of the nine patients achieved CR, one patient achieved PR, two patients had no remission, and one patient relapsesed[10] (Table 3). Another case series included six patients treated with RTX (four weekly doses of 375 mg/m2); five patients achieved CR, and one achieved PR[11] (Table 3). No serious adverse events were reported in either of the studies.

Based on these reports and our clinical experience, RTX is useful for inducing and maintaining remission in adult patients with initial MCD. The initial dose of RTX was different in the published reports. In the Guan N series, all the patients received small doses of RTX. In Fenoglio R's series and our series, all patients received a higher dose regimen, and the results showed that all but one patient experienced sustained remission over a prolonged follow-up and did not require repeated infusions. It is worth discussing whether a higher initial dose regimen can lead to protracted remission.

Discussion

However, the underlying pathogenesis of MCD is not yet fully understood. Although MCD has long been recognized as a T cell-mediated disease, the role of B cells in MCD has gained attention owing to the successful use of B cell-depleting agents. Recently, MCDs were reported to have several functions. 1) Production of pathogenic antibodies: The Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCHL1) antibody causes podocyte detachment in vitro and is associated with the relapse of idiopathic NS in mice[12]. Nephrin autoantibodies, which are present in almost 1/3 of patients with MCD, may cause loss of slit diaphragm architecture and are associated with disease activity[13]. 2) B cells are involved in the pathogenesis of MCD, possibly by producing cytokines such as IL-4. In a murine model, local activation of B cells induced foot effacement and proteinuria through the production of IL-4[14]. 3) B-cell depletion may lead to a new balance between T cell subsets. One study showed that RTX-treated patients had a low frequency of variant natural killer T (iNKT) and might induce qualitative alterations in CD4+ follicular T cells (TFH cells), thus inhibiting the reconstitution of switched memory B cells, which has been associated with steroid-dependent MCD disease activity [15, 16]. With more attention paid to the role of B cells in MCD, B cell depletion agents are widely used in the treatment of frequently relapsing/steroid-dependent MCD[8, 17], and have achieved good clinical results. However, it is unknown how these drugs function during the first MCD episode.

Based on limited case reports, RTX has shown efficacy and an acceptable safety profile as a first-line induction regimen in adults with MCD. In our series, one patient was treated with obinutuzumab (OTZ) (two doses of 1,000 mg), a type II humanized anti-CD20 monoclonal antibody. According to previous reports, fully human and humanized anti-CD20 antibodies demonstrate stronger in vitro activities than RTX, and OTZ may offer some advantages over RTX[18]. In a recent case series, OTZ was effective in membranous nephropathy that failed to respond to RTX[19]. In MRL/lpr mice, a murine model of Lupus, OTZ was more effective in depleting B cells than RTX[20]. A Randomized Controlled Study showed that OTZ provided a longer sustained clinical benefit than RTX in Proliferative Lupus Nephritis[20]. The patient achieved PR in the first month, CR in the third month, and sustained remission for one year. Notably, his peripheral CD19+ cells remained depleted for longer than those in the other four patients. One study showed that the proportion of CD19 recovery in patients with relapse is higher[8, 21]. However, another study showed that ofatumumab (a fully human anti-CD20 monoclonal antibody) was not superior to RTX in maintaining MCD remission in children and young adults, although ofatumumab treatment resulted in more prolonged depletion of B cells[22]. Whether fully human and humanized anti-CD20 antibodies are superior to RTX for the initial treatment of MCD requires further investigation.

The optimal initial dose of anti-CD20 antibodies for adults with MCD remains unknown. At present, there are no reports on the application of OTZ in MCD. Different dosing protocols of RTX include 1) one, two, three, or four weekly rituximab infusions of 375 mg/m2[23-27]. 2) 500 mg 2 weeks apart[28]. 3) One gram, once or on days 1 and 15[25] is frequently used for relapsing/steroid-dependent MCD. However, these studies showed no correlation between the different treatment regimens or conclusions could not be drawn owing to the small size of the treatment subgroups. Studies on RTX administered alone as front induction therapy in adult MCD are rare. Therefore, it is difficult to determine the optimal initial dose based on the current results because of the limited number of patients treated. Hence, controlled trials are urgently needed to compare the different dosing protocols for MCD.

Another key issue is that the optimal dosing timing for RTX re-administration to maintain remission remains unclear. Studies have shown that the risk of relapse is associated with B-cell reconstitution after RTX[8, 21]. Other studies have shown that remission may persist despite complete B-cell recovery, and relapse can occur in the presence of sustained depletion of B cells[21, 29, 30]. In our study, Patient 1 relapsed six months after RTX infusion, while CD19+B cells were still undetectable. The remaining four patients reached CR and were relapse-free, even with CD19+ B-cell recovery. Hence, it is not accurate to determine the timing of administration based on whether the B cells are reconstructed. However, further studies are required to confirm these results.

Adverse reactions to anti-CD20 antibodies should be considered. Among the patients included in this study,

no serious side effects that might have been caused by RTX or OTZ were observed. The most common concerns revolve around infusion reactions such as hypotension and allergies. These issues could be addressed by using supportive drugs and adopting slow infusion. Regarding long-term adverse reactions to RTX, one study showed that RTX as induction and maintenance therapy in ANCA-associated vasculitis was followed for an average of 2.1 years, and no significant adverse reactions were observed[31]. In another study on lupus nephritis, OTZ did not carry a higher risk of serious adverse events or infections at 52 weeks of follow-up[32]. All patients were administered anti-CD20 antibodies alone, and the longest follow-up period was 37 months with no recurrence or adverse reactions. Therefore, RTX and OTZ showed favorable long-term safety profiles.

This study has some limitations. The number of patients was small because anti-CD20 antibodies as a first-line treatment for MCD are limited owing to the higher out-of-pocket costs. Moreover, there was no control group in this study, and there remains needs for further studies whether anti-CD20 antibody as first-line treatment for MCD are superior to steroids in terms of therapeutic efficacy and adverse effects in first-line treatment of MCD. All patients in this study achieved CR regardless of whether they were treated with OTZ or RTX, and only one patient relapsed. Whether humanized anti-CD20 has any advantage over chimeric mAbs in the treatment of MCD remains unclear.

Conclusion

In conclusion, the extremely positive results obtained with anti-CD20 monoclonal antibody in the first episode of MCD suggest the possibility of considering this regimen as first-line treatment, providing more options for patients with steroid contraindications. Several key questions remain to be addressed in future clinical trials, including whether anti-CD20 antibody is superior to steroids, the optimal dosing and timing for repeated infusion to maintain CR, and whether humanized anti-CD20 should be preferred over chimeric monoclonal antibodies.

Author Contributions

Writing – original draft: ShuangXi Li.

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Declaration of conflicting interests

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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Data availability statement

All relevant data are within the paper and its Supporting Information files.

Patient anonymity and informed consent

Written informed consent was obtained from all the participants prior for the publication of this case report.

Ethical Compliance

The study was approved by the ethics committee of Chang Hai Hospital.

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