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Treatment Of The Minimal Change Disease In Adult

Yaghoubi F.MD

TUMS , Shariati Hospital

Introduction

- Minimal change disease (MCD) is a common pathological type of nephrotic syndrome, accounting for approximately 90% of idiopathic nephrotic syndrome in children

- In adults, MCD represents about 10% - 15% of patients with idiopathic nephrotic syndrome .

- 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) .

Introduction

- KDIGO guidelines, the traditional treatment approach for MCD typically involves the administration of corticosteroids, specifically oral prednisone.

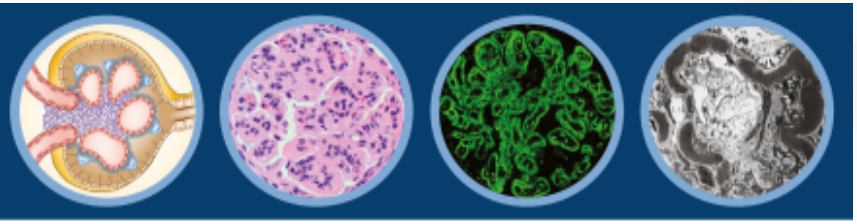
- Prednisone is commonly used as the initial therapy due to its anti-inflammatory and immunosuppressive properties.

- The standard treatment protocol for MCD consists of an initial high-dose phase, 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.

Introduction

- 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 .
- 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 .
- In 2002, there was the first report suggesting the use of RTX in patients with primary membranous nephropathy (remission rates ranging from 57% to 89% in PMN).



Minimal Change Disease

Marina Vivarelli, Laura Massella,* Barbara Ruggiero,† and Francesco Emma**

Abstract

Minimal change disease (MCD) is a major cause of idiopathic nephrotic syndrome (NS), characterized by intense proteinuria leading to edema and intravascular volume depletion. In adults, it accounts for approximately 15% of patients with idiopathic NS, reaching a much higher percentage at younger ages, up to 70%–90% in children >1 year of age. In the pediatric setting, a renal biopsy is usually not performed if presentation is typical and the patient responds to therapy with oral prednisone at conventional doses. Therefore, in this setting steroid-sensitive NS can be considered synonymous with MCD. The pathologic hallmark of disease is absence of visible alterations by light microscopy and effacement of foot processes by electron microscopy. Although the cause is unknown and it is likely that different subgroups of disease recognize a different pathogenesis, immunologic dysregulation and modifications of the podocyte are thought to synergize in altering the integrity of the glomerular basement membrane and therefore determining proteinuria. The mainstay of therapy is prednisone, but steroid-sensitive forms frequently relapse and this leads to a percentage of patients requiring second-line steroid-sparing immunosuppression. The outcome is variable, but forms of MCD that respond to steroids usually do not lead to chronic renal damage, whereas forms that are unresponsive to steroids may subsequently reveal themselves as FSGS. However, in a substantial number of patients the disease is recurrent and requires long-term immunosuppression, with significant morbidity because of side effects. Recent therapeutic advances, such as the use of anti-CD20 antibodies, have provided long-term remission off-therapy and suggest new hypotheses for disease pathogenesis.

Clin J Am Soc Nephrol 12: 332–345, 2017. doi: 10.2215/CJN.05000516

*Division of Nephrology and Dialysis, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; and †Clinical Research Center for Rare Diseases "Aldo e Cele Daccò", IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Ranica, Bergamo, Italy

Correspondence: Dr. Marina Vivarelli, Division of

Initial Treatment

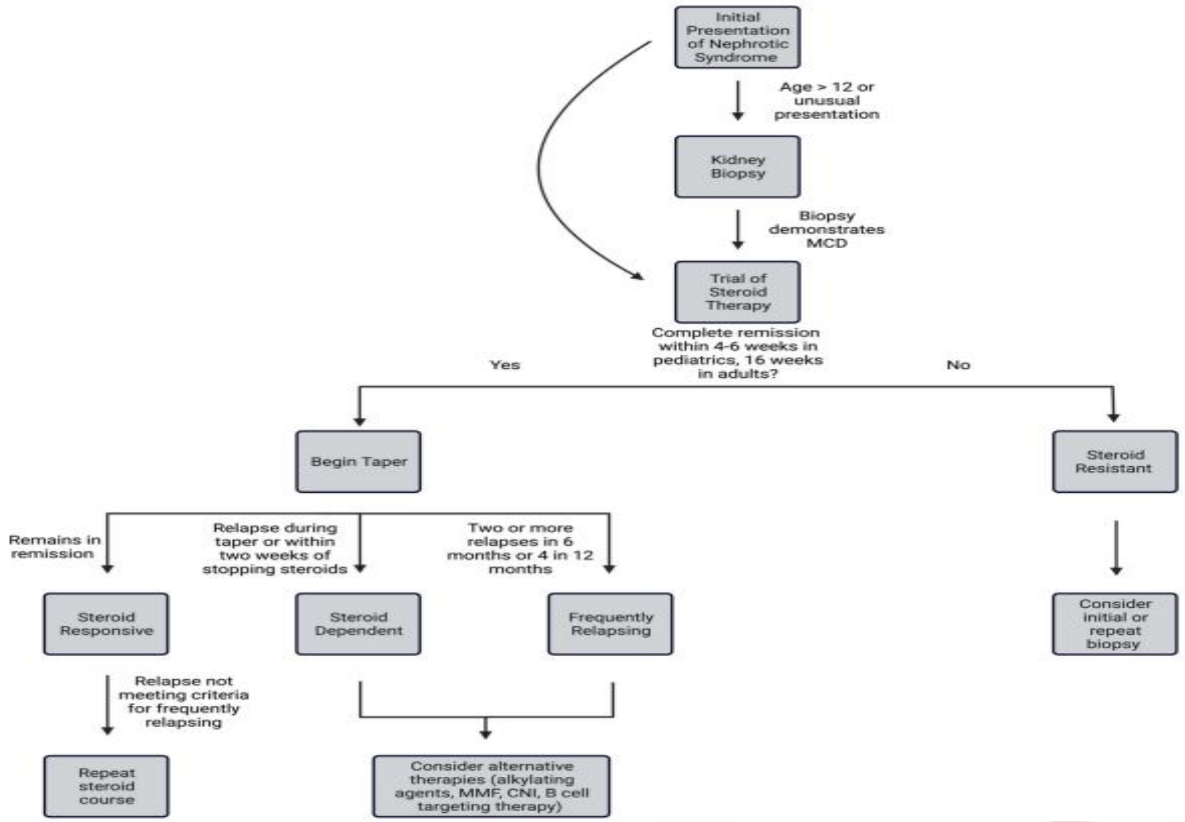
- Therefore, the currently accepted induction regimen of 1 mg/kg per day (maximum 80 mg/d) or 2 mg/kg every other day (maximum 120 mg/d) for 16 weeks (minimum 4 weeks if remission is promptly achieved)

- Previous studies failed to show a significant benefit of intravenous methylprednisolone (20 mg/kg per day for 3 days) followed by reduced-dose oral steroids (prednisone 0.5 mg/kg per day) versus full-dose oral steroids alone (prednisone 1 mg/kg per day).

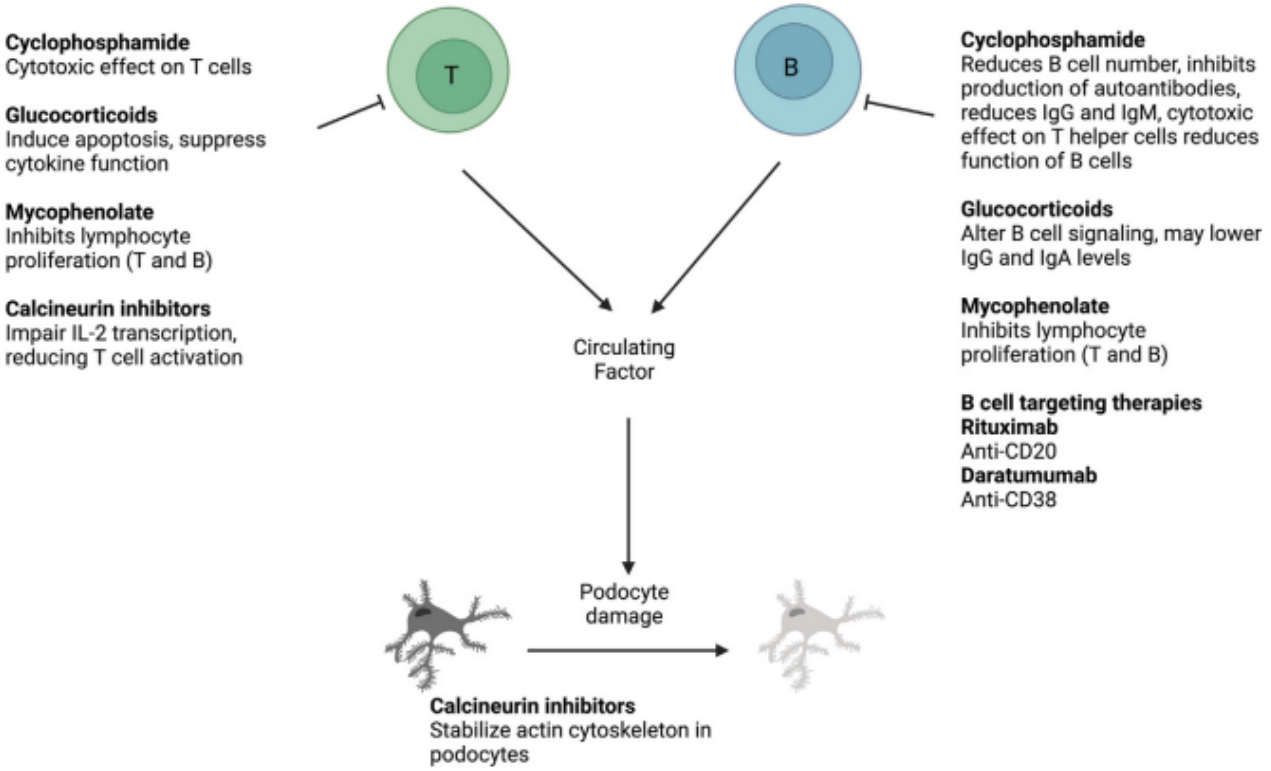
- A reasonable compromise may be to taper prednisone by 5–10 mg/wk after remission over 8 weeks for a total 24-week period of exposure to prednisone

Marina Vivarelli, Laura Massella, Barbara Ruggiero. Minimal Change Disease . Clin J Am Soc Nephrol 12: 332–345, February, 2017

Initial management of suspected minimal change disease



Mechanisms of therapies in minimal-change disease



Adv in Kidney Disease and Health **2024**;31(4):267-274

Steroid-Resistant Forms

- 10%–20% of cases of adult MCD are steroid resistant, defined as no response to 16 weeks of oral prednisone daily or alternate days, and in these patients a **second renal biopsy may reveal FSGS**.

- Treatment of steroid-resistant MCD should follow KDIGO guidelines for steroid-resistant FSGS .

- Genetic forms are much rarer than in children, but should be investigated in young adults and in the presence of positive family history, particularly regarding ACTN4 mutations.

- The mainstay of therapy in these patients are calcineurin inhibitors, but cyclophosphamide, both oral and intravenous, has also been used and proved effective in some patients .

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Steroid-Resistant Forms

- An open-label trial comparing TAC versus intravenous cyclophosphamide showed an effective and more rapid induction of remission by TAC .
- MMF, chlorambucil, azathioprine, ACTH, and **rituximab** have been used only in the setting of small case series with variable results.
- The use of alkylating agents or calcineurin inhibitors in frequently relapsing NS or steroid-dependent NS is determined on the basis of clinical studies in children or small observational studies in adults.
- In adults, cyclophosphamide was shown to be better than CsA in steroid dependent NS, and even more in frequently relapsing NS, in maintaining remission .

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Steroid-Resistant Forms

- In a randomized controlled trial by Ponticelli et al. on 75 adults and children with frequently relapsing NS and steroid-dependent NS (31 were MCD), long-term outcome was better with cyclophosphamide versus CsA, with 63% patients maintaining remission after 2 years compared with 25% with CsA .

- On the other hand, adding CsA to steroids was found to induce remission more rapidly than steroids alone at first relapse .

- The optimal **CsA** dose is not established, however, KDIGO guidelines suggest a **3–5 mg/kg** per day range on the basis of dosages used in these studies.
- Some patients may relapse once CsA is discontinued.

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Steroid-Resistant Forms

- MMF use has been reported only in small patient cohorts, showing efficacy in about 60%–70% of patients.

- **KDIGO guidelines suggest to use cyclophosphamide as a first-line therapy for frequently relapsing NS or steroid-dependent NS, or alternatively CsA, to preserve fertility and MMF only in patients intolerant to the other drugs** .

- Also, **rituximab** has proven to be effective in adults, and data from another frequent cause of nephrotic syndrome in adults, membranous nephropathy, in which rituximab is used as single agent, are encouraging even considering the long-term safety.

Marina Vivarelli, Laura Massella, Barbara Ruggiero. Minimal Change Disease . Clin J Am Soc Nephrol 12: 332–345, February, 2017

Definitions on the basis of references and on the authors' clinical experience

Nephrotic Syndrome
- Edema
- Massive proteinuria (>40 mg/m^2 per h in children, >3.5 g/d in adults)
- Hypoalbuminemia (<2.5 g/dl)

Remission
- Resolution of edema
- Normalization of serum albumin (≥3.5 g/dl)
- Marked reduction in proteinuria
- Complete remission (<4 mg/m^2 per h or negative dipstick in children, <0.3 g/d in adults)
- Partial remission (<2 g/1.73 m^2 per d, decreased by 50% and serum albumin ≥2.5 g/dl in children, <3.5 g/d and decreased by 50% in adults)

Relapse
- Recurrence of massive proteinuria (>40 mg/m^2 per h in children, >3.5 g/d in adults)
- Positive urine dipstick (≥3+ for 3 d or positive for 7 d, usually applicable to children)
- ±Edema

Steroid-Sensitive Nephrotic Syndrome
- Response to PDN 60 mg/m^2 per d within 4–6 wk ±MPD boluses in children
- Response to PDN 1 mg/kg per d or 2 mg/kg every other d, within 16 wk in adults

Nonrelapsing Nephrotic Syndrome
- No relapses for >2 yr after the end of therapy for the first episode of nephrotic syndrome (applicable to children, not yet defined in adults)

Infrequently Relapsing Nephrotic Syndrome
- <2 relapses per 6 mo (or <4 relapses per 12 mo)

Frequently Relapsing Nephrotic Syndrome
- ≥2 relapses per 6 mo (or ≥4 relapses per 12 mo)

Steroid-Dependent Nephrotic Syndrome
- Relapse during steroid therapy or within 15 d of discontinuation

Steroid-Resistant Nephrotic Syndrome
- No response to PDN 60 mg/m^2 per d within 4 wk ±MPD boluses in children
- No response to PDN 1 mg/kg per d or 2 mg/kg every other d, within 16 wk in adults

Multidrug-Resistant Nephrotic Syndrome
- Poorly defined as absence of partial remission after 6 mo OR absence of complete remission after 2 yr
- Treatment often consists of MPD boluses + oral prednisone for 6 mo + CsA and, in some cases, rituximab. Other protocols are also used

PDN, prednisone; MPD, methylprednisolone; CsA, cyclosporine A.

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Therapy procedures for adults

First Episode of Nephrotic Syndrome[a]

PDN 1 mg/kg per d or 2 mg/kg every other d (maximum 80 mg/d or 120 mg every other d) for 4–16 wk (evidence level 2C)

Taper slowly over a total period of up to 6 mo after achieving remission[b] (evidence level 2D)

Infrequent relapses

PDN 1 mg/kg per d or 2 mg/kg every other d (maximum 80 mg/d or 120 mg every other d) for 4–16 wk (evidence level 2C)

Taper slowly over a total period of up to 6 mo after achieving remission[b] (evidence level 2D)

Frequent relapses and steroid dependency[c]

CPA 2–2.5 mg/kg per d for 8 wk (single course) (evidence level 2C)

If relapse occurs despite CPA or to preserve fertility:

CsA 3–5 mg/kg per d in two divided doses for 1–2 yr (evidence level 2C)

Or TAC 0.05–0.1 mg/kg per d in two divided doses until 3 mo after remission, then tapered to the minimum efficient dose for 1–2 yr (evidence level 2C)

If intolerant to PDN, CPA, and CsA or TAC:

MMF 500–1000 mg twice daily for 1–2 yr (evidence level 2D)

PDN, prednisone; CPA, cyclophosphamide; CsA, cyclosporine A; TAC, tacrolimus; MMF, mofetil mycophenolate.

[a]During first episode, statins for hypercholesterolemia and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers for proteinuria in normotensive subjects are not indicated.

[b]Taper by 5–10 mg/wk (it is preferable not to exceed a total maximum steroid exposure of 24 mo).

[c]In patients with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome who develop steroid-related side effects (evidence level 1B).

Marina Vivarelli, Laura Massella, Barbara Ruggiero. Minimal Change Disease . Clin J Am Soc Nephrol 12: 332–345, February, 2017

Rituximab in the Treatment of Adult Minimal Change Disease

Possible mechanisms of rituximab treatment in minimal change disease

- 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, including **B cell depletion, indirect/direct effects on T cells, and direct effects on podocytes.**

Yin Zheng, Hu Haofei and Wan Qijun. Mechanisms and Clinical Research Progress of Rituximab in the Treatment of Adult Minimal Change Disease**. Journal of Clinical Nephrology 2023**; 57-62.

Possible mechanisms of rituximab treatment in minimal change disease

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

- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)
- Direct effects on abnormal B lymphocytes

2. Effects on T Lymphocytes(RTX blocks T cell co-stimulatory pathways in MCD, thereby **modulating T cell function& regulate Treg cells** (these cells may impact disease relapse in nephrotic syndrome)

3. Direct effects on podocytes(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.**

Yin Zheng, Hu Haofei and Wan Qijun. Mechanisms and Clinical Research Progress of Rituximab in the Treatment of Adult Minimal Change Disease. Journal of Clinical Nephrology 2023; 57-62.

Rituximab for idiopathic membranous nephropathy

Giuseppe Remuzzi, Carlos Chiurchiu, Mauro Abbate, Verusca Brusegan, Mario Bontempelli, Piero Ruggenenti

Treatments for idiopathic membranous nephropathy, a common cause of nephrotic syndrome, can be very toxic. In view of the pathogenic potential of B cells in this disease, we studied the effects of four weekly infusions of rituximab (375 mg/m^2)— the monoclonal antibody to B-cell antigen CD20—in eight patients who had idiopathic membranous nephropathy with persistent nephrotic syndrome. At weeks 4 and 20, urinary protein decreased from mean (SE) 8·6 g/24 h (1·4) to 3·8 (0·8) and 3·7 (0·9), respectively (p<0·0001). At week 20, albuminuria and albumin fractional clearance decreased by 70% and 65%, and serum albumin increased by 31%. CD20 B lymphocytes fell below normal ranges up to study end. The short-term risk-benefit profile of rituximab seems more favourable to that of any other immunosuppressive drug used to treat idiopathic membranous nephropathy.

Lancet 2002; **360:** 923–24

Current therapeutic approaches to idiopathic membranous nephropathy (IMN), the most common cause of nephrotic syndrome in adults in many countries, still rely on steroids and immunosuppressant drugs, which are not fully specific and carry the risk of severe toxic effects. Over the past 30 years, the outcome of IMN has not substantially improved; up to 40% of patients can develop end-stage renal failure after treatment with glucocorticoids, alkylating agents, and other drugs. The long-term effectiveness of ciclosporin is also questionable due to the high relapse rates and associated toxic effects of the drug.[1,2]

Advances in the understanding of pathogenetic mechanisms of disease in IMN should help to find specific approaches that are more likely to be effective and safe in the long term. Proteinuria is a major independent indicator of disease progression. Data from studies in animals suggest that the typical subepithelial immune deposits in glomeruli are caused by B-cell-mediated reactions, which promote injury to the glomerular filtering barrier and result in proteinuria.[3] Thus, although IMN autoantigens remain elusive and the role of B cells has not been fully explained in man, agents that specifically interfere with B cells would ideally represent the first step toward selective therapy. The success of such treatments would also provide evidence for the role of a B-cell-related mechanism in IMN.[4]

Therefore, we investigated the efficacy and safety profile of rituximab (Roche SpA, Monza, Italy), a monoclonal antibody against the cell surface antigen CD20 of B cells,[5] in three men and four women with IMN. Patients' average age was 52 years (range 24–75). They had creatinine clearance greater than 20 mL/min/1·73 m^2, persistent urinary protein excretion rate greater than 3·5 g/24 h for at least 6 months, and were on full-dose angiotensin-converting-enzyme (ACE) inhibitors and without remission over 29·7 (13–49) months from renal biopsy. Patients gave written informed consent to study participation according to the declaration of Helsinki. Seven patients were on diuretics or statins (or both), two were on non-dihydropyridine calcium-channel blockers, three were on aspirin, and one was on oral anticoagulant therapy.

We gave the patients intravenous infusions of rituximab (375 mg/m^2) every 4 weeks. No change in diet or concomitant treatment was introduced during the 20 weeks of follow-up. Proteinuria (primary efficacy variable) and other clinical and laboratory variables were measured at baseline, weekly during the treatment period, and every 4 weeks from week 4 to week 20. Data with skewed distribution were log-transformed before analysis. Comparisons were by paired Student's *t* test and correlations by Spearman's rank.

During the treatment period, urinary proteins significantly and non-linearly decreased in all patients (tables 1 and 2). Two patients achieved full remission (proteinuria ≤1 g/24 h) and three achieved part remission (≤3·5 g/24 h). At study end, proteinuria had decreased by 62%, albuminuria by 70%, and albumin fractional clearance by 65%, whereas serum albumin had increased by 31% versus baseline, associated with a reduction in serum cholesterol (table 2). At each visit from week 8 to 20, serum albumin increase was associated with a decrease in albumin fractional clearance (Spearman's r=−0·73, p=0·04; −0·69, p=0·06; −0·76, p=0·03; −0·78, p=0·02, at weeks 8, 12, 16, and 20, respectively).

Pediatr Nephrol (2008) 23:1269–1279
DOI 10.1007/s00467-008-0814-1

ORIGINAL ARTICLE

Rituximab treatment for severe steroid- or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases

Vincent Guigonis · Aymeric Dallocchio · Véronique Baudouin · Maud Dehennault · Caroline Hachon-Le Camus · Mickael Afanetti · Jaap Groothoff · Brigitte Llanas · Patrick Niaudet · Hubert Nivet · Natacha Raynaud · Sophie Taque · Pierre Ronco · François Bouissou

Received: 12 December 2007 / Revised: 16 February 2008 / Accepted: 18 February 2008 / Published online: 9 May 2008

Abstract Several case reports suggest that rituximab (RTX) could be effective in steroid-dependent nephrotic syndrome, but RTX efficacy has not yet been studied in a series of patients. Safety and efficacy of RTX were assessed in a multicenter series of 22 patients aged 6.3–22 years with severe steroid-dependent nephrotic syndrome or steroid-resistant but cyclosporin-sensitive idiopathic nephrotic syndrome. Patients were treated with two to four infusions of RTX. Seven patients were nephrotic at the time of RTX treatment. Peripheral B cells were depleted in all subjects. Remission was induced in three of the seven proteinuric patients. One or more immunosuppressive (IS) treatments could be withdrawn in 19 patients (85%), with no relapse of proteinuria and without increasing other IS drugs. RTX was effective in all patients when administered during a proteinuria-free period in association with other IS agents. When relapses occurred, they were always associated with an increase in CD19 cell count. Adverse effects were observed in 45% of cases, but most of them were mild and transient. This study suggests that RTX could be an effective treatment for severe steroid-dependent nephrotic syndrome.

Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children

Koichi Kamei · Shuichi Ito · Kandai Nozu · Shuichiro Fujinaga · Makiko Nakayama · Mayumi Sako · Mari Saito · Maki Yoneko · Kazumoto Iijima

Received: 12 February 2009 / Revised: 25 March 2009 / Accepted: 26 March 2009 / Published online: 7 May 2009

Abstract We conducted a multicenter prospective trial to evaluate the efficacy, safety and pharmacokinetics of a single dose of rituximab (375 mg/m^2 body surface area) for the treatment of children with refractory steroid-dependent nephrotic syndrome (SDNS). All patients (n=12) were able to discontinue steroids at a median of 74 days after treatment. The frequency of relapses per 6 months was significantly reduced and the steroid-free period per 6 months was significantly increased after treatment compared with those before treatment. The condition in nine of the patients (75%) relapsed at a median of 129 days after treatment, and seven patients were given additional rituximab due to steroid dependency. Most of the relapses developed simultaneously with recovery of B-cells. However, three patients (25%) did not have a relapse with B-cell recovery and the disease was kept in remission for more than 1 year. None of the patients developed life-threatening adverse events. This is the first report of a prospective study of a single dose of rituximab for refractory SDNS. Treatment with a single dose of rituximab may be effective for refractory SDNS, but its efficacy to prevent relapses was transient in most of the patients.

Keywords Refractory steroid-dependent nephrotic syndrome · Children · Clinical trial · Rituximab · Pharmacokinetics

Introduction

Idiopathic nephrotic syndrome is the most frequent glomerular disease of childhood. Most cases respond to steroid treatment, but approximately 40% of the children develop

Nephrol Dial Transplant (2013) 28: 1225–1232
doi: 10.1093/ndt/gfs515
Advance Access publication 13 December 2012

Effect of single-dose rituximab on steroid-dependent minimal-change nephrotic syndrome in adults

ABSTRACT

Background. Steroid-dependent minimal-change nephrotic syndrome (MCNS) requires administration of prolonged courses of prednisolone (PSL); therefore, a paradigm shift from such toxic 'non-specific' therapies to selective immunomodulating regimens is necessary for these cases.

Methods. To assess the therapeutic effects of rituximab (an anti-CD20 antibody) in adult patients with steroid-dependent MCNS, we performed a prospective trial of the effects of a single dose of rituximab administered twice at an interval of 6 months in 25 MCNS patients. We evaluated the biochemical parameters and compared the clinical findings between the 12-month period before and 12-month period after the first rituximab infusion.

Results. A significant reduction in the number of relapses and the total dose and the maintenance dose of PSL administered was observed during the 12-month period after the first rituximab infusion when compared with the findings during the 12-month period before the first rituximab infusion [25 (100%) versus 4 (16%), $P < 0.001$; 8.2 versus 3.3 g, $P < 0.001$; 26.4 mg/day at baseline versus 1.1 mg/day at 12-month, $P < 0.0001$]. Complete remission was achieved/maintained in all patients undergoing B-cell depletion. Four of 17 patients with B-cell repletion developed relapse.

Conclusions. Our results revealed that rituximab therapy was associated with a reduction in the number of relapses and in the total dose of PSL needed. Therefore, rituximab appears to be a useful therapeutic agent for adult patients with steroid-dependent MCNS. These results suggest that this treatment is rational and should be considered as an important option in the management of adult patients with steroid-dependent MCNS.

INTRODUCTION

Patients with steroid-dependent minimal-change nephrotic syndrome (MCNS) are usually treated with steroids and

Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome

Piero Ruggenenti,*† Barbara Ruggiero,* Paolo Cravedi,* Marina Vivarelli,‡ Laura Massella,‡ Maddalena Marasà,† Antonietta Chianca,* Nadia Rubis,* Bogdan Ene-Iordache,* Michael Rudnicki,§ Rosa Maria Pollastro,‖ Giovambattista Capasso,‖ Antonio Pisani,¶ Marco Pennesi,** Francesco Emma,‡ and Giuseppe Remuzzi,*† for the Rituximab in Nephrotic Syndrome of Steroid-Dependent or Frequently Relapsing Minimal Change Disease Or Focal Segmental Glomerulosclerosis (NEMO) Study Group

*IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri," Clinical Research Center for Rare Diseases "Aldo e Cele Daccò," Ranica, Bergamo, Italy; †Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; ‡Division of Nephrology and Dialysis, Children's Hospital Bambino Gesù, IRCCS, Rome, Italy; §Department of Nephrology and Hypertension, Medical University, Innsbruck, Austria; ‖Department of Nephrology, Second University of Naples, Naples, Italy; ¶Department of Nephrology, Federico II University, Naples, Italy; and **Institute for Maternal and Child Health - IRCCS "Burlo Garofolo," Trieste, Italy

ABSTRACT

The outcome of steroid-dependent or frequently relapsing nephrotic syndrome of minimal change disease (MCD), mesangial proliferative GN (MesGN), or FSGS may be poor and with major treatment toxicity. This academic, multicenter, off-on trial (ClinicalTrials.gov #NCT00981838) primarily evaluated the effects of rituximab therapy followed by immunosuppression withdrawal on disease recurrence in 10 children and 20 adults with MCD/MesGN (n=22) or FSGS who had suffered ≥2 recurrences over the previous year and were in steroid-induced remission for ≥1 month. Participants received one dose (n=28) or two doses of rituximab (375 mg/m^2 intravenously). At 1 year, all patients were in remission: 18 were treatment-free and 15 never relapsed. Compared with the year before rituximab treatment, total relapses decreased from 88 to 22 and the per-patient median number of relapses decreased from 2.5 (interquartile range [IQR], 2–4) to 0.5 (IQR, 0–1; P<0.001) during 1 year of follow-up. Reduction was significant across subgroups (children, adults, MCD/MesGN, and FSGS; P<0.01). After rituximab, the per-patient steroid maintenance median dose decreased from 0.27 mg/kg (IQR, 0.19–0.60) to 0 mg/kg (IQR, 0–0.23) (P<0.001), and the median cumulative dose to achieve relapse remission decreased from 19.5 mg/kg (IQR, 13.0–29.2) to 0.5 mg/kg (IQR, 0–9.4) (P<0.001). Furthermore, the mean estimated GFR increased from 111.3±25.7 to 121.8±29.2 ml/min per 1.73 m^2 (P=0.01), with the largest increases in children and in FSGS subgroups. The mean height z score slope stabilized in children (P<0.01). Treatment was well tolerated. Rituximab effectively and safely prevented recurrences and reduced the need for immunosuppression in steroid-dependent or frequently relapsing nephrotic syndrome, and halted disease-associated growth deficit in children.

J Am Soc Nephrol 25: 850–863, 2014. doi: 10.1681/ASN.2013030251

Glomerular Diseases

Review Article

Glomerular Dis 2023;3:211–219
DOI: 10.1159/000533695

Received: December 30, 2022
Accepted: August 14, 2023
Published online: August 18, 2023

Review of the Role of Rituximab in the Management of Adult Minimal Change Disease and Immune-Mediated Focal and Segmental Glomerulosclerosis

Ahsan Aslam[a] Abbal Koirala[b]

[a]Division of Nephrology and Hypertension, Assistant Professor of Clinical Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [b]Division of Nephrology, Clinical Assistant Professor of Medicine, University of Washington, Seattle, WA, USA

Keywords
Rituximab · Nephrotic syndrome · Minimal change disease · Focal and segmental glomerulosclerosis · Complete remission · Partial remission · Steroid-dependent nephrotic syndrome · Steroid-resistant nephrotic syndrome · Corticosteroids · Calcineurin inhibitors · Urine protein-to-creatinine ratio

Abstract
Background: Minimal change disease and primary FSGS are podocytopathies but are also immune-mediated diseases. Rituximab acts via multiple mechanisms by tilting the balance between autoreactive B and T cells in favor of regu-

rituximab is not very promising in adult steroid-resistant nephrotic syndrome. Although ofatumumab would cause prolonged B-cell depletion and is fully humanized, it is unclear if it is superior to rituximab in preventing relapse of nephrotic syndrome. ***Key Messages:*** Rituximab therapy can induce prolonged remission in adults with frequently relapsing and steroid-dependent nephrotic syndrome. However, no good data exist on using rituximab in steroid-resistant nephrotic syndrome.

Introduction

Rituximab in the treatment of adult frequently relapsing and steroid-dependent MCD (remission rates)

Author	Setting	Sample size	Previous failed t reatments	RTX dose	CR, *n* (%)	Follow-up, months
Cortazar et al. [23] (2019), USA	Retrospective, single-center study	8 MCD	Pred, CsA, FK, MMF, Abat, Cyc, Aza	9 g (7.5–11 g), 1 g IV dose, 4-month interval	7/8 (87.5)	35 (19–57)
King et al. [24] (2017), UK	Retrospective, single-center study	13 MCD	Pred, CsA, FK, MMF, Cyc, Lev, rapamycin, sirolimus	2 × 1 g, 2 weeks apart	12/13 (92.3)	20 (6–85)
Brown et al. [25] (2017), USA	Retrospective, single-center study	5 MCD	Pred, CsA, FK, MMF, Cyc	2 × 1 g 2–3 weeks interval	5/5 (100)	39.5 (20–80)
Miaybe et al. [26] (2016), Japan	Retrospective, single-center study	10 MCD	Pred, CsA, FK, MMF, Cyc, MZ	4 × 375 mg/m^2 (10), 6-month interval	10/10 (100)	24
Bruchfield et al. [27] (2014), Sweden	Retrospective, single-center study	16 MCD	Pred, CsA, FK, MMF, Cyc, MZ	2 × 500 mg (8), 2 × 1 g (3), 3 × 375 mg/m^2 (1), 4 × 375 mg/m^2 (4)	13/16 (81.3)	44 (12–70)
Guitard et al. [28] (2014), France	Prospective, multicenter study	41 MCD	Pred, CsA, FK, MMF, Cyc, Aza	1 × 1 g (1), 2 × 1 g (21), 2 × 1 g (5), 3 × 375 mg/m^2 (2), 4 × 375 mg/m^2 (12)	25/41 (61)	39 (6–71)
Iwabuchi et al. [29] (2014), Japan	Prospective, single-center study	25 MCD	Pred, CsA, FK, MMF, Cyc, MZ	4 × 375 mg/m^2, 6-month interval	25/25 (100)	24
Takei et al. [30] (2013), Japan	Prospective, single-center study	25 MCD	Pred, MMF, CsA, MZ	2 × 375 mg/m^2 (25), 6-month interval	25/25 (100)	12
Munyentwali et al. [31] (2013), France	Retrospective, single-center study	17 MCD	Pred, CsA, FK, MMF, Cyc, Aza, Lev, chlorambucil	1 × 375 mg/m^2 (1), 2 × 375 mg/m^2 (7), 3 × 375 mg/m^2 (4), 4 × 375 mg/m^2 (3)	15/17 (88.2)	29.5 (5.1–82.2)
Kong et al. [32] (2013), Australia	Retrospective, single-center study	7 MCD	Pred, CsA, FK, MMF, Cyc, Aza, chlorambucil	1 × 500 mg, 1 × 600 mg, 4 × 600 mg, 1 × 700 mg, 2 × 700 mg	6/7 (85.7)	31.5 (15–44)
Hoxha et al. [33] (2011), Germany	Prospective, single-center study	6 MCD	Pred, CsA, FK, MMF, Cyc, Aza, Lev	1 × 375 mg/m^2	5/6 (83.3)	17.2±4.8

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Relapse rates of MCD studies with rituximab treatment

Author	Setting	Sample size	Previous failed treatments	RTX dose	Relapse rate, *n* (%)	Follow-up, months
Cortazar et al. [23] (2019), USA	Retrospective, single-center study	8 MCD	Pred, CsA, FK, MMF, Abat, Cyc, Aza	9 g (7.5–11 g), 1 g IV dose, 4-month interval	0/8 (0)	35 (19–57)
Iwabuchi et al. [34] (2018), Japan	Retrospective, single-center study	19 MCD	Pred, CsA, FK, MMF, Cyc, MZ	4 × 375 mg/m^2, 6-month interval	4/19 (21.1)	24
Katsuno et al. [35] (2019), Japan	Retrospective, single-center study	8 MCD	Pred, CsA, FK, MMF, Cyc, MZ	1 × 500 mg (3), 2 × 500 mg (3), 3 × 500 mg (1), 3,100 mg (1, seven times)	3/8 (37.5)	13.9 (11.6–20)
-Da Silva et al. [36] (2017), Spain	Retrospective, multicenter study	22 MCD	Pred, CsA, FK, MMF, Cyc	1 × 1 g (10), 2 × 1 g (9), 3 × 1 g (5), 4 × 1 g (4), 1,788±704 mg	4/22 (18.2)	31±26
King et al. [24] (2017), UK	Retrospective, single-center study	13 MCD	Pred, CsA, FK, MMF, Cyc, Lev, rapamycin, sirolimus	2 × 1 g, 2 weeks apart	7/13 (53.8)	20 (6–85)
Brown et al. [25] (2017), USA	Retrospective, single-center study	5 MCD	Pred, CsA, FK, MMF, Cyc	2 × 1 g 2–3 weeks interval	2/5 (40)	39.5 (20–80)
Papakrivopoulou et al. [37] (2016), UK	Prospective, single-center study	15 MCD	Pred, CsA, FK, MMF, Cyc, Aza, Lev	2 × 1 g, 6 months apart, 1–3 g	5/15 (33.3)	43
Dekkers et al. [38] (2015), The Netherlands	Retrospective, single-center study	10 MCD	Pred, CsA, FK, MMF, Cyc	2 × 375 mg/m^2	3/10 (30)	43±23.5
Miyabe et al. [26] (2016), Japan	Retrospective, single-center study	54 MCD	Pred, CsA, FK, MMF, Cyc, MZ	4 × 375 mg/m^2 (25), 6-month interval	12/54 (22.2)	24
Bruchfield et al. [27] (2014), Sweden	Retrospective, single-center study	16 MCD	Pred, CsA, FK, MMF, Cyc, MZ	2 × 500 mg (8), 2 × 1 g (3), 3 × 375 mg/m^2 (1), 4 × 375 mg/m^2 (4)	7/16 (43.8)	44 (12–70)
Guitard et al. [28] (2014), France	Prospective, multicenter study	41 MCD	Pred, CsA, FK, MMF, Cyc, Aza	1 × 1 g (1), 2 × 1 g (21), 2 × 1 g (5), 3 × 375 mg/m^2 (2), 4 × 375 mg/m^2 (12)	18/41 (43.9)	39 (6–71)
Iwabuchi et al. [29] (2014), Japan	Prospective single-center study	25 MCD	Pred, CsA, FK, MMF, Cyc, MZ	4 × 375 mg/m^2, 6-month interval	7/25 (28)	24
Takei et al. [30] (2013), Japan	Prospective single-center study	25 MCD	Pred, MMF, CsA, MZ	2 × 375 mg/m^2 (25), 6-month interval	4/25 (16)	12
Munyentwali et al. [31] (2013), France	Retrospective, single-center study	17 MCD	Pred, CsA, FK, MMF, Cyc, Aza, Lev, chlorambucil	1 × 375 mg/m^2 (1), 2 × 375 mg/m^2 (7), 3 × 375 mg/m^2 (4), 4 × 375 mg/m^2 (3)	6/17 (35.3)	29.5 (5.1–82.2)

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Standard Dosing of RTX in MCD and FSGS

- There is no standard dosing for RTX.
- **Most studies have used 375 mg/m2 /week for 1–4 weeks** (adopted from lymphoma dosing).
- Some studies have used 1 g 2 weeks apart.
- **We often use 1 g 2 weeks apart in patients with frequently relapsing and steroid-dependent nephrotic syndrome due to ease of administration in the outpatient setting.**

Other Anti-CD20 Antibodies in MCD and FSGS

- RTX has murine variable regions in light and heavy chains, but the Fc portion is humanized .
- Both **ofatumumab** and **obinutuzumab** are fully humanized mAbs, which reduces unintended immune responses against the therapies.
- They all differ in their ability to eliminate CD20 B cells via different mechanisms (direct killing, antibody-dependant phagocytosis, complement-dependent cytotoxicity, and antibody dependent cell-mediated cytotoxicity .
- **RTX is known to bind to the long loop of the CD20 receptor, whereas ofatumumab binds to both short and long loops of CD20, causing prolonged B-cell depletion .**
- Ofatumumab has been used to treat refractory membranous nephropathy .

Anti-CD20 Antibodies in MCD and FSGS

- Ravani et al. conducted a randomized controlled trial in children and adults (age 2–24) with steroid-dependent nephrotic syndrome.
- The median age was 11; all were maintained in remission with corticosteroids and calcineurin inhibitors.
- The baseline characteristics were creatinine 0.5 mg/dL, albumin 4 g/dL, UPCR 80 mg/d, and GFR 146 mL/min/ 1.73 m2 .
- One hundred forty patients were randomized to a single dose of ofatumumab (1,500 mg/1.73 m2) or RTX (375 mg/m2).
- Steroids and CNI were withdrawn within 60 days of RTX and ofatumumab infusions.

Anti-CD20 Antibodies in MCD and FSGS

- The relapse rates at 12 months (51.4% vs. 52.8%) and 24 months (65.7% vs. 75.7%) were not different between RTX and ofatumumab.
- There was a trend toward earlier relapse with ofatumumab in patients less than 9 years of age.
- B-cell depletion was more prolonged with ofatumumab, and anti-RTX antibodies developed over time in the RTX group, but they had no bearing on the risk of relapse.

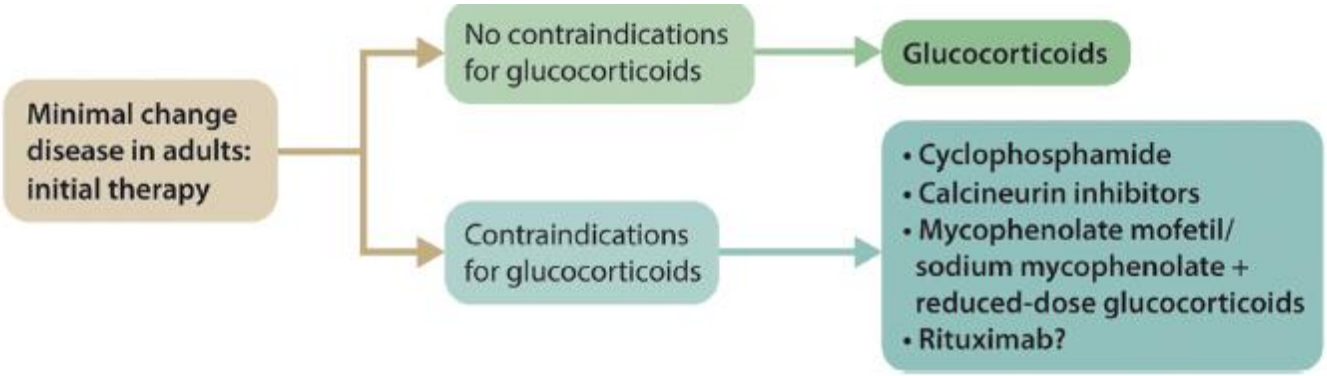
Anti-CD20 Antibodies in MCD and FSGS

- RTX has been used extensively in children and adults with frequently relapsing and steroid-dependent nephrotic syndrome.
- Most of the evidence in adults is observational, and randomized controlled trials are lacking. Presently, favorable data regarding the role of RTX in steroid-resistant nephrotic syndrome is sparse.
- Although ofatumumab would cause prolonged B-cell depletion and is fully humanized, it is unclear if it is superior to RTX in preventing relapse of nephrotic syndrome.
- More studies are required to clarify the role of ofatumumab, so presently, ofatumumab is only used in cases of RTX allergy in nephrotic syndrome due to MCD and FSGS.

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.

CONCLUSION


Minimal change disease in adults: initial therapy
No contraindications for glucocorticoids
Glucocorticoids
Contraindications for glucocorticoids
• Cyclophosphamide
• Calcineurin inhibitors
• Mycophenolate mofetil/ sodium mycophenolate + reduced-dose glucocorticoids
• Rituximab?

CONCLUSION

- Glucocorticoids remain the mainstay of therapy, recent advances have provided important first steps toward determining the underlying mechanism of disease in some patients, which may in turn allow us to provide more targeted therapy in the future and, for now, may help guide the use of alternative therapies in cases of steroid dependence or frequently relapsing disease.


THANKS FOR YOUR
ATTENTION