# Rituximab in Glomerulonephritis

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Rituximab is a chimeric monoclonal antibody directed against the CD20 receptor on B cells present along all maturational stages of its cycle but not in .plasma cells

The administration of one dose of 375 mg/m2 per week for 4 weeks or the administration of a total dose 2 g within a 2-week interval causes depletion of circulating B lymphocytes, which lasts for 6–7 .months

- Although rituximab was designed for the treatment of relapsing or refractory non-Hodgkin lymphoma B

- it was considered an attractive drug for the treatment .of various autoimmune diseases mediated by antibodies

# Rituximab in MCD

Although most of the patients with nephrotic syndrome related to MCD will respond to corticosteroid therapy, up to a third will become corticosteroid-dependent or have a .frequently relapsing disease

For this subset of patients, current guidelines suggest using other regimens such as oral cyclophosphamide, calcineurin inhibitors (CNIs) (tacrolimus or cyclosporine), or mycophenolate mofetil (MMF)

.Historically, MCD has been considered a lymphocyte T-cell pathology

However, recent advances in our understanding of the pathways involved in the pathogenesis of the disease identified a more complex pathogenesis with participation of innate immunity, B-cells, and regulatory T-cells

The first case that reported the use of rituximab in the management of .MCD in adults was in 2007

- In this report, a patient with a multirelapsing nephrotic syndrome secondary to MCD (30 relapses)

y/o women, >30 relapse since 6 yrs, failure to respond to all other 23• potentially steroid-sparing drugs (CPA, CsA, MMF)

w RTX >>> long-term remission 3 w after 4•

! still at 28 mo

Francois H et al, Unexpected efficacy of RTX in multirelapsing MCD in the adult: the first case report, Am J Kidney Dis, 2007

Following these case reports, several retrospective and .prospective trials have been published

In one retrospective case series, 17 patients with steroid-dependent or frequently relapsing MCD despite several immunosuppressive therapy were treated with rituximab . and analyzed

Rituximab achieved a sustained response with no relapse in . 65% of patients after 2 years

No infectious or hematologic complications were observed during follow-up

Munyentwali H et al. Rituximab is an efficient and safe treatment in adults with steroid-dependent minimal change disease. *Kidney Int*. 2013;83(3):511–516

In another retrospective analysis involving 41 patients with , steroid-dependent or multiple relapsing MCD

rituximab achieved complete clinical response in 61% of patients, .and a partial clinical response in 17%

Twenty-two percent of patients did not respond to rituximab .therapy

No serious adverse events were noted secondary to rituximab .treatment

Guitard J, Hebral AL, Fakhouri F, et al. Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance. *Nephrol Dial . Transpl*. 2014;29(11):2084–2091

In a prospective trial involving 25 patients with steroid-dependent MCD, rituximab was administered twice at 6 months .interval, at a dose of 375 mg/m2

All patients were on prednisolone, 20 patients were on .cyclosporine A, three patients were on MMF

Twelve months after the first rituximab infusion only four patients remained on prednisolone, and only six patients .remained on cyclosporine

Furthermore, the mean doses of both prednisolone and cyclosporine A were reduced significantly

Most of the relapses developed simultaneously with the recovery of the B-cell count (CD19 or CD20), supporting that suppression .of B-cell is involved in the pathophysiology of MCD

Takei T, Itabashi M, Moriyama T, et al. Effect of single-dose rituximab on steroid-dependent minimal-change nephrotic syndrome in adults. *Nephrol Dial Transpl*. 2013;28(5):1225–1232

In summary, current evidence supports the use of rituximab in steroid-dependent and frequently relapsing MCD

however, properly designed randomized controlled trials (RCTs) are needed to establish the superiority and safety of rituximab as compared to other currently used agents in this setting, such as cyclophosphamide, cyclosporine, and . MMF

# Rituximab in FSGS

- The 2012 KDIGO guidelines recommend the use of corticosteroids as first-line therapy for idiopathic FSGS
- Patients who remain resistant to steroids after at least 4 months, are treated with cyclosporine or high dose dexamethasone with MMF.
- According to KDIGO, available evidence was insufficient to support the use of rituximab in FSGS.
- Only few reports have evaluated the use of rituximab in adult patients with FSGS, with variable results.

Fernandez-Fresnedo et al reported the use of rituximab in 8 patients with FSGS resistant to steroids and other .therapies

Only two patients had a sustained and significant reduction in proteinuria at 1 year and one patient had a significant .but transient effect

All other five patients failed to respond to rituximab .therapy

Fernandez-Fresnedo zet al. Rituximab treatment of adult patients with steroid-resistant . focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol*. 2009;4(8):1317–1323

- In another report from Japan, two patients with steroid-resistant FSGS did not respond to a single dose of .rituximab
- However, two patients with steroid-dependent FSGS achieved complete remission after a single dose of rituximab, which allowed discontinuation of steroids .and CNIs

Ochi A, Takei T, Nakayama K, et al. Rituximab treatment for adult patients with . focal segmental glomerulosclerosis. *Intern Med*. 2012;51(7):759–762

rituximab was administered to 30 patients with steroid-.dependent or frequently relapsing idiopathic FSGS

Over 1 year observation period, relapses decreased by approximately fivefold compared with the year preceding .rituximab treatment

Ruggenenti P, Ruggiero B, Cravedi P, et al; Rituximab in Steroid-Dependent or Frequently Relapsing Focal Segmental Glomerulosclerosis (NEMO) Study Group. *J Am Soc Nephrol*. . 2014;25(4):850–863

: Oct 15;8(55) 2017 Oncotarget.

# Rituximab treatment in adults with focal .segmental glomerulosclerosis

have described our experience treating 15 FSGS patients with .steroid-dependent with RTX

Patients received RTX (375 mg/m2) intravenously on days 1, 8, 23, .and 29

During a median follow-up of 8 months (range, 3-36 months) after RTX administration, all patients achieved complete or partial .remission

Relapses decreased by approximately 30-fold compared with the year preceding RTX treatment, and an 89.27% reduction in .proteinuria was observed

Furthermore, RTX treatment could decrease medical costs by 76.52% compared with the costs associated with the long-term .use (for 12-13 months) of steroids and immunosuppressive drugs

In conclusion, RTX treatment was safe and effective for patients .with refractory FSGS

.108–113:(2)46;2017 Am J Nephrol.

# High-Dose Rituximab Ineffective for Focal Segmental .Glomerulosclerosis: A Long-Term Observation Study

.University of Turin, Turin, Italy

Eight patients who had biopsy-proven FSGS ( range 40-81 years) with major risk factors precluding corticosteroids or conventional immunosuppression were treated with a high dose of RTX (8 weekly doses of 375 mg/m2) and prospectively followed up for at least 2 .years (range 24-42 months)

**:RESULTS**

RTX failed to improve proteinuria in 7 out of 8 patients, who had persistent nephrotic proteinuria. Only one patient showed an improvement in renal function and a remarkable reduction in . proteinuria

There were no differences in clinical or laboratory characteristics or in the CD20 B lymphocyte count after RTX between the responder and .the 7 nonresponder patients

**:CONCLUSIONS**

Only a minority (1 of 8) of adult patients with FSGS showed positive . effects of high doses of RTX

- In summary, currently available evidence do not support a role for rituximab in the management of FSGS .
- RCTs are warranted to assess the possible benefit of rituximab in the management of steroid-dependent and frequently relapsing FSGS .

# Rituximab in IgAN

IgAN is the most common form of idiopathic
. glomerulonephritis worldwide

Current guidelines, however, recommend antiproteinuric and antihypertensive therapy with ACEIs or ARBs as an initial therapeutic approach in IgAN patients with persistent proteinuria of .1 g/day, and a 6-month course of corticosteroids if the former approach was not successful .after 3–6 months

Combination immunosuppressive therapy and the addition of cyclophosphamide and azathioprine was not advocated except in cases of rapidly progressive crescentic .glomerulonephritis

- In a prospective, a single dose of rituximab at 375 mg/m2 was given to treat 24 patients with IgAN .
- After 6 months , there was no significant change in proteinuria .
- The results of this trial was limited by the short follow-up of 6 months, and the possible need for several doses of rituximab to achieve response in a slowly progressive disease like IgAN .

Sugiura H, Takei T, Itabashi M, et al. Effect of single-dose rituximab on primary glomerular diseases: *Nephron Clin Pract*. 2011;117(2) :

Results of a prospective, multicenter, randomized, controlled trial: rituximab in the treatment of .progressive IgA nephropathy

patients with biopsy-proven IgAN, and proteinuria 54 of .1 g/day, while on an ACEI, ARB, will be randomized to rituximab 1 g, on days 1, 15, 168, and 182, or to .placebo

Change in proteinuria and kidney function will be .assessed at 12 months

rituximab did not significantly improve renal function or proteinuria

Fernando Fervenza, Mayo Clinic. Rituximab in progressive IgA nephropathy. ClinicalTrials.gov [database on the Internet]. Accessed July 2, 2016

.Apr;28(4):1306-1313 2017 J Am Soc Nephrol.

## A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction

In this multicenter study conducted over 1-year follow-up, randomized 34 patients with IgA nephropathy and proteinuria >1 g/d, maintained on an ACEI, ARB and eGFR<90 ml/min, to receive standard therapy or rituximab with standard therapy. Primary outcome measures included .change in proteinuria and change in EGFR

Treatment with rituximab depleted B cells and was well .tolerated

.eGFR did not change in either group

Rituximab did not alter the level of proteinuria compared with that at baseline or in the control group; three patients . in each group had ≥50% reduction in level of proteinuria

In this trial, rituximab did not significantly improve renal function or proteinuria assessed over 1 year

# Rituximab in idiopathic MPGN

- Few reports described the use of rituximab in idiopathic MPGN. In one study , two patients with idiopathic MPGN received rituximab. Patients achieved partial remission 29 months after a single dose of rituximab
- In a prospective trial six patients with MPGN two doses of rituximab were administered at 1 g on days 1 and 15. The two patients achieved complete remission after 12 months, while the four patients achieved partial remission

Kong WY, Swaminathan R, Irish A. Our experience with rituximab therapy for adult-onset . primary glomerulonephritis and review of literature. *Int Urol Nephrol*. 2013;45(3):795–802

Dillon JJ, Hladunewich M, Haley WE, Reich HN, Cattran DC, Fervenza FC. Rituximab. 36 therapy for Type I membranoproliferative glomerulonephritis. *Clin Nephrol*. 2012;77(4):290–295

# Rituximab in idiopathic MN

.The earliest report was published in 2002 by Remuzzi et al

In this study, four weekly doses of rituximab (375 mg/$m^2$) were given to eight patients with IMN who had nephrotic range proteinuria (>3.5 g/24 h) for at least 6 months without remission, despite full-dose angiotensin-.converting-enzyme inhibitors (ACEI)

Mean proteinuria decreased from 8.6 g to 3.8 g/24 h . during the treatment period

patients achieved complete remission (proteinuria <1 2 .g/24 h), and 3 patients achieved partial remission

The efficacy of rituximab in the setting of CNI-dependent .IMN was assessed in a small pilot prospective study

Thirteen with GFR >60 mL/min were given 4 weekly doses . of rituximab (375 mg/$m^2$)

As a result, proteinuria decreased significantly at 6 months. CNIs and other immunosuppressant drugs could be stopped . in all patients

Three patients relapsed but responded to a repeated .course of rituximab

. At 30 months, all patients were in remission

Segarra A, Praga M, Ramos N, et al. Successful treatment of membranous glomerulonephritis with rituximab in calcineurin inhibitor-dependent patients. . *Clin J Am Soc Nephrol*. 2009;4(6):1083–1088

In a nonrandomized study, Ruggenenti et al prospectively monitored the outcomes of 100 consecutive patients with IMN .treated with 4 weekly rituximab infusion

patients had already been treated with steroids alone or in 32 combination with alkylating agents, CNIs, or other . immunosuppressant

At baseline evaluation, median proteinuria was 9.1 g/24 h. Median duration of proteinuria before rituximab administration was 25.5 and 65.4 months for the 32 patients with second-line therapy

Over a median follow-up of 29 months after rituximab .administration, 65 patients achieved complete or partial remission

. The median time to remission was 7.1 months

Similar proportion of patients achieved complete or partial remission among those given rituximab as first-line or second-line .therapy

Rituximab was well tolerated and there was no treatment-related adverse events

Ruggenenti P, Cravedi P, Chianca A, et al. Rituximab in idiopathic membranous nephropathy. *J . Am Soc Nephrol*. 2012;23(8):1416–1425

GEMRITUX was a prospective, multicenter, RCT at 31 French hospitals. 77 patients with IMN and nephrotic syndrome despite 6 months of nonimmunosuppressive antiproteinuric treatment (NIAT) were randomized to either continue NIAT alone or the addition of .rituximab 375 mg/$m^2$ on days 1 and 8

At 6 months there was no difference between the two groups with regards of complete or partial remission, as 13 patients in the NIAT-rituximab group and 8 patients in the NIAT group, achieved either .complete or partial remission

Rituximab achieved PLA2R-Ab depletion in 56% of patients after 3 months

Another important finding was  after rituximab, suggesting that PLA2R-Ab depletion may be a strong predictor of response to . rituximab therapy

In contrast, B-cell depletion did not predict response to rituximab .therapy

In the extended observational period of the trial (up to 24 months), significantly more patients in the NIAT-rituximab group achieved partial or complete remission as compared to NIAT group (64.9% and 34.2%) There was no difference in side effects between .the two groups

Dahan K, Debiec H, Plaisier E, et al; GEMRITUX Study Group. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. *J Am Soc Nephrol*. . Epub 2016 Jun 27

.Jun;11(3):337-341 2018 Clin Kidney J.

**Low-dose Rituximab therapy in resistant idiopathic membranous .nephropathy: single-center experience**

Rituximab (RTX) therapy has given encouraging results in IMN, but most of the studies have used a higher dose, which is limited by the high cost as well as a potential increased risk of infections

**: Methods**

A total of 21 patients with treatment-resistant IMN treated with RTX from 2015 to 2016 received two doses of RTX (500 mg each) infusion 7 days apart. CD19 count was performed after 4 weeks. A single dose of RTX was repeated .after 4-6 weeks if CD19 count was not depleted

**: Results**

All the patients were non-responders to prior immunosuppressive treatment. Twenty (95.2%) patients achieved targeted CD19 depletion with two doses of RTX. One patient required one additional RTX dose due to inadequate B-cell suppression. A total of 13 (61.9%) patients achieved remission with RTX therapy: 4 (19.0%) complete and 9 (42.9%) partial remission

Renal survival was significantly better in patients who responded to RTX .therapy as compared with those who did not achieve remission (P = 0.0037)

**: Conclusion**

Low-dose RTX therapy is effective and safe in immunosuppression-resistant IMN

# Rituximab in idiopathic MN

- In summary, rituximab may be an effective alternative in the management of IMN .

- However, more RCTs with longer follow-up are still needed to confirm the benefit and safety of rituximab both as first-line or second-line therapy as compared to the commonly used regimens of corticosteroids/cyclophosphamide, cyclosporine, and tacrolimus .