Rituximab in Glomerulonephritis

Elham Ramezanzadeh
Assistant professor of nephrology
GUMS

- MN
- SLE
- AAV
- MCD
- FSGS
- IgA Nephropathy
- MPGN(Ig mediated and complement mediated)

- Membranous nephropathy (MN) is the most common cause of primary nephrotic syndrome in adults.
- Secondary causes ….. 20% of all MN cases.
- primary MN, is the focus of this review.
- The natural course of MN is heterogeneous...
- half of the patients attain spontaneous remission over a period of 5 to 10 years, and the other half….
- Mtype PLA2R autoantibody ……..70% to 80% of patients.
- autoantibodies directed against thrombospondin type-1 domain-containing 7A can be identified.
- neural epidermal growth factor-like 1 protein and semaphorin 3b w

(PLA2R) as target antigen …… a rationale for B-cell depleting agents such as rituximab.

The efficacy of rituximab in inducing remission has been investigated in several studies, including 3 randomized controlled trials, in which complete and partial remission of proteinuria was achieved in approximately two-thirds of treated patients.

Due to its favorable safety profile, rituximab is now considered a first-line treatment option for MN, especially in patients at moderate and high risk of deterioration in kidney function.

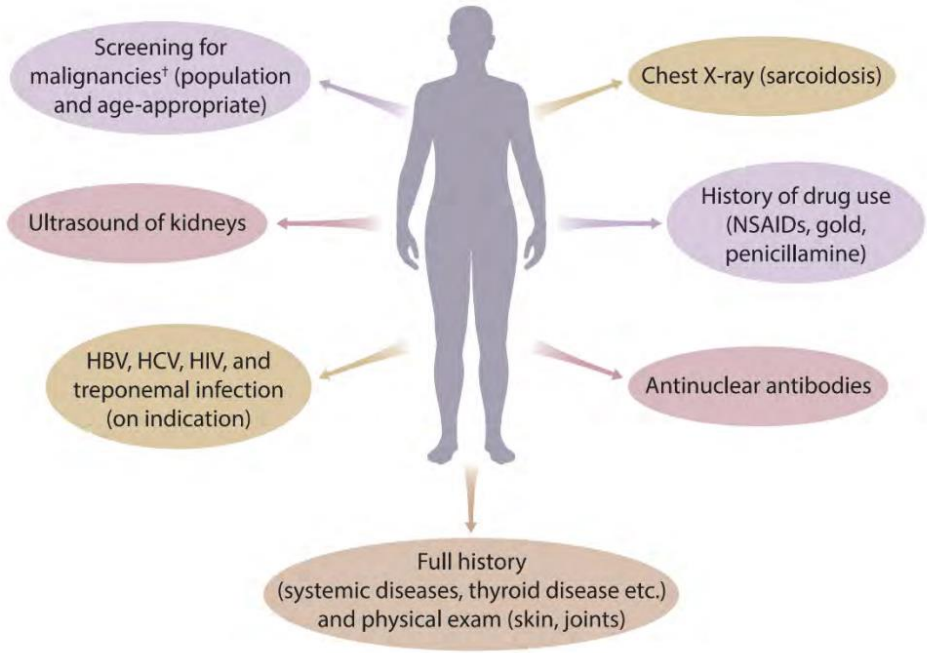
CHAPTER 3. MEMBRANOUS NEPHROPATHY

3.1. Diagnosis

Practice Point 3.1.1. A kidney biopsy may not be required to confirm the diagnosis of MN in patients with a compatible clinical and serological presentation.

Practice Point 3.1.2. Patients with MN should be evaluated for associated conditions, regardless of whether PLA2Rab and/or TSHD7Aab are present or absent (Figure MN3).

*Figure MN3. Evaluation of patients with MN for associated conditions**



HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NSAIDs, nonsteroidal anti-inflammatory drugs

*Patient with MN should be evaluated for associated conditions, independent of the presence or absence of PLA2Rab or TSHD7Aab

†Varies per country; the yield of cancer screening is not very high especially in younger patients. Many centers will perform chest X-ray or CT scan, look for iron deficiency, and require the patients to have to participate in the national screening program for breast and colon cancer; a PSA test is done in adult males >50-60 years.

Table MN1. Clinical criteria for assessing risk of progressive loss of kidney function‡

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and/or serum albumin >30 g/L	• Normal eGFR, proteinuria >4 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB • PLA2Rab <50 RU/ml† • Mild low molecular weight proteinuria • Selectivity index <0.15 • U IgG <250 mg/d	• eGFR <60 ml/min/1.73m²* • Proteinuria >8 g/d for >6 months • PLA2Rab >150 RU/ml† • High low molecular weight proteinuria • U IgG >250 mg/d • Selectivity index >0.20	• Life-threatening nephrotic syndrome • Rapid deterioration of kidney function not otherwise explained • High low molecular weight proteinuria in two urine samples collected with interval of 6–12 months

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; PLA2Rab, antibodies against the M-type phospholipase-A2-receptor

*Most studies have used SCr values to guide management, and SCr values >1.5 mg/dl are often used to define kidney insufficiency. An eGFR value of 60 ml/min/1.73 m^2 defines kidney insufficiency in a young adult. It is important to realize that eGFR decreases with age, and an SCr value of 1.5 mg/dl reflects an eGFR of 50 ml/min/1.73 m^2 in a 60-year-old male patient and 37 ml/min/1.73 m^2 in a 60-year-old female patient. Thus, when using eGFR in risk estimation, age should be taken into account.

†Cut-off values are not validated. PLA2Rab should be measured at 3- to 6-month intervals, the shorter interval being performed in patients with high PLA2Rab levels at baseline. Changes in PLA2Rab levels during follow-up likely add to risk estimation. Disappearance of PLA2Rab precedes clinical remission and should lead to refraining from additional therapy. Detailed data are lacking.

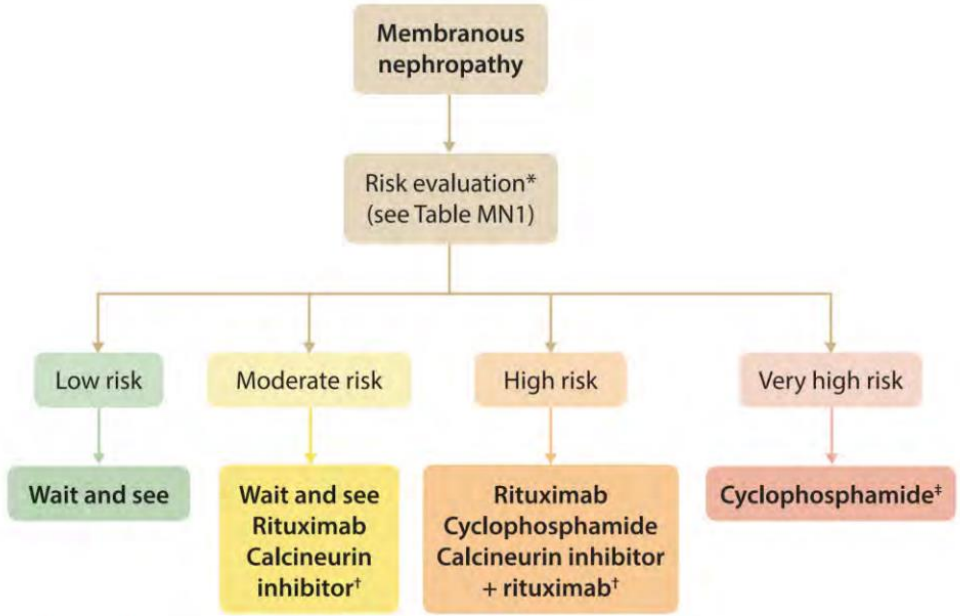
‡eGFR and PCR are used in routine clinical care. Other biomarkers may not be available in all centers; this table provides an overview of useful biomarkers.

3.3. Treatment

Practice Point 3.3.1. Considerations for treatment of patients with primary MN:

- **All patients with primary MN and proteinuria should receive optimal supportive care.**
- **Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury (Figure MN4).**

Figure MN4. Risk-based treatment of MN

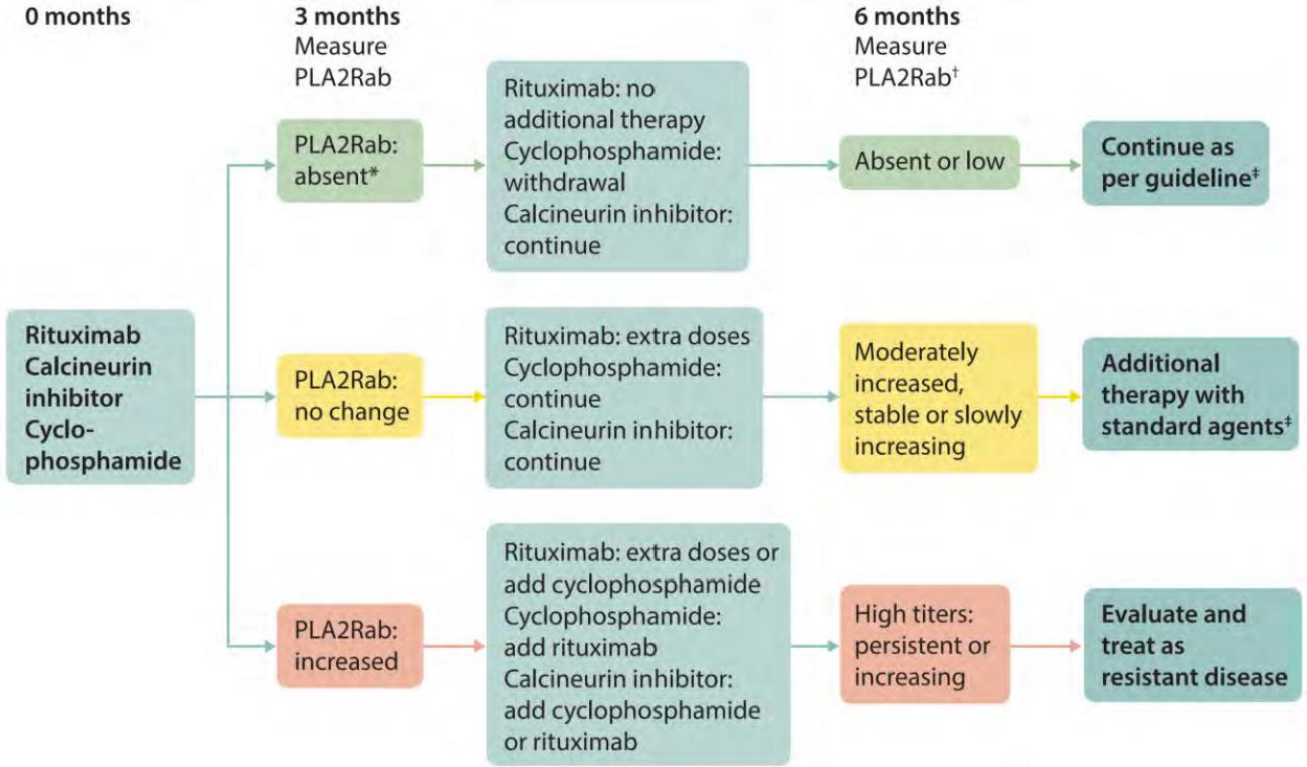


*See Practice Point 3.2.1 and Table MN1 for a detailed description of risk evaluation.

†CNI monotherapy is considered less efficient. Treatment with CNI for 6-12 months with rapid withdrawal is associated with a high relapse rate. Still, its use may be considered in patients with normal eGFR and moderate risk of progression, since many of these patients will develop a spontaneous remission. The use of CNI will shorten the period of proteinuria. In patients with high risk of progression, addition of rituximab after six months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of PLA2Rab after CNI treatment.

‡There is insufficient evidence that rituximab used in standard doses prevents development of kidney failure. In patients who do not tolerate or can no longer use cyclophosphamide, consultation with an expert center is advised.

Figure MN5. Immunological monitoring in MN after start of therapy



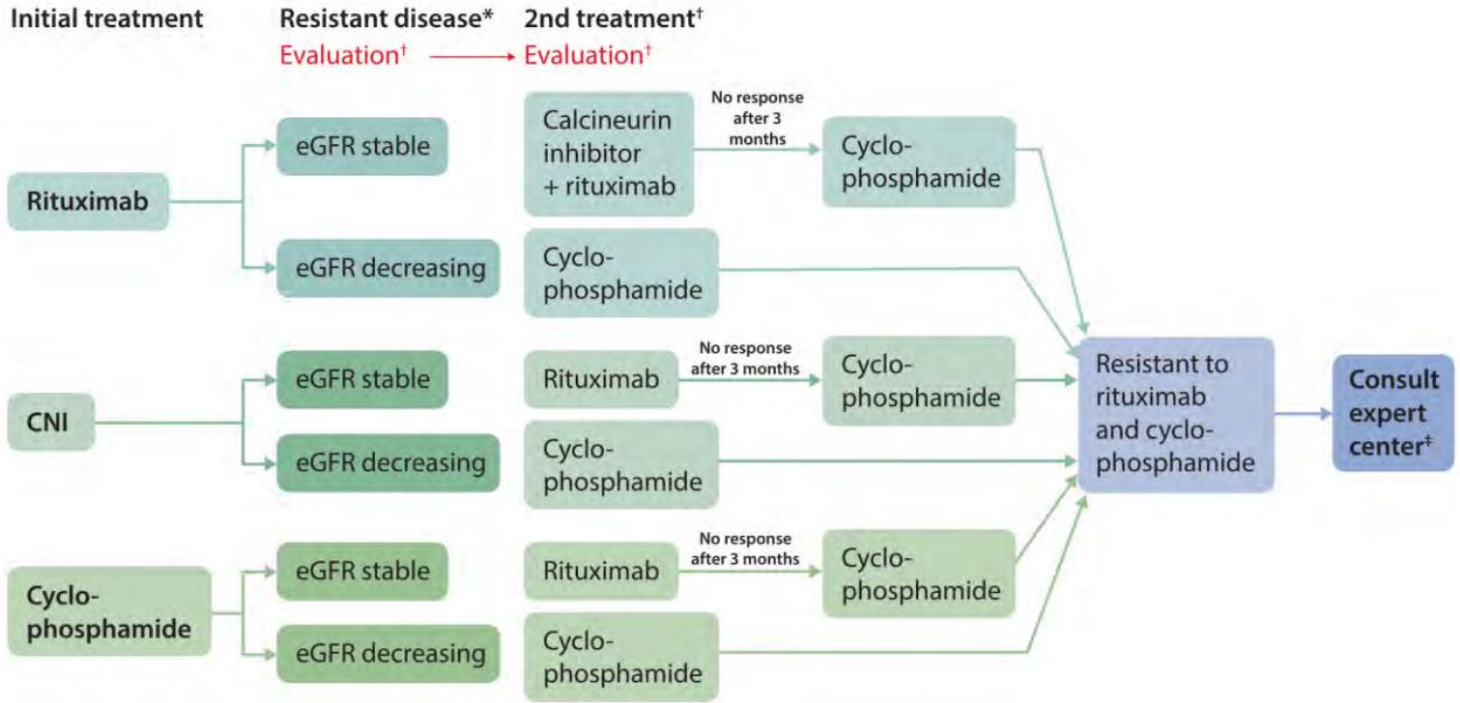
PLA2Rab, antibodies against the M-type phospholipase-A2-receptor

*A large decrease in PLA2Rab levels may indicate a good clinical response. Although there are no defined cut-off values, many experts consider reductions of 50-90% to represent a large decrease in PLA2Rab levels.

†This algorithm is simplified to allow easy decision-making. The course may be less well-defined or more difficult to interpret in many patients. However, if it is impossible to classify a patient as a good responder or resistant to disease, we suggest consulting an expert center.

‡See text for current treatment schedules. NB: the cumulative dose of cyclophosphamide should not exceed 25 g (approximately six months of therapy at a dose of 1.5 mg/kg/day). Lower doses (maximum 10g) must be used in patients who wish to conceive. CNI are unlikely to induce late immunological remission; in patients with persistent PLA2Rab, these drugs may be used in combination with rituximab. B-cell depletion is insufficient to judge the efficacy of rituximab therapy; extra doses may be considered even if B-cells in the peripheral blood are absent or very low. However, in these patients, consultation with an expert center is advised.

Figure MN7. Management of resistant disease[§]



CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate

*Evaluation: In patients with resistant disease, compliance should be checked and efficacy monitored (e.g., B cell response, anti-rituximab antibodies, IgG levels, leukocytopenia during cyclophosphamide, CNI levels). Persistent proteinuria is not sufficient to define resistance. If proteinuria persists, while serum albumin has increased, one should consider secondary FSGS. This would be further supported by the disappearance of PLA2Rab. In patients with persistent proteinuria with normal or near-normal serum albumin levels or patients with persistent proteinuria despite loss of PLA2Rab, a kidney biopsy should be considered to document active membranous nephropathy.

†Second treatment is dependent on the severity of deterioration of eGFR as indicated. When rituximab is chosen as second treatment, the response of proteinuria and PLA2Rab should be evaluated after three months. Cyclophosphamide treatment should take into account the maximal tolerable dose: the cumulative dose should not exceed 10 g if preservation if fertility is required. The cumulative dose should not exceed 25 g to limit risk of malignancies. Expert centers may still use more, based on weighing risk and benefits.

‡Patients who did not respond to rituximab or cyclophosphamide should be consulted with an expert center. These centers may choose experimental therapies (bortezomib, daratumumab, antibody to CD38 antibody, and belimumab) or a higher dose of conventional immunosuppressive therapy.

§Details of commonly used treatment regimens are shown in Table MN2

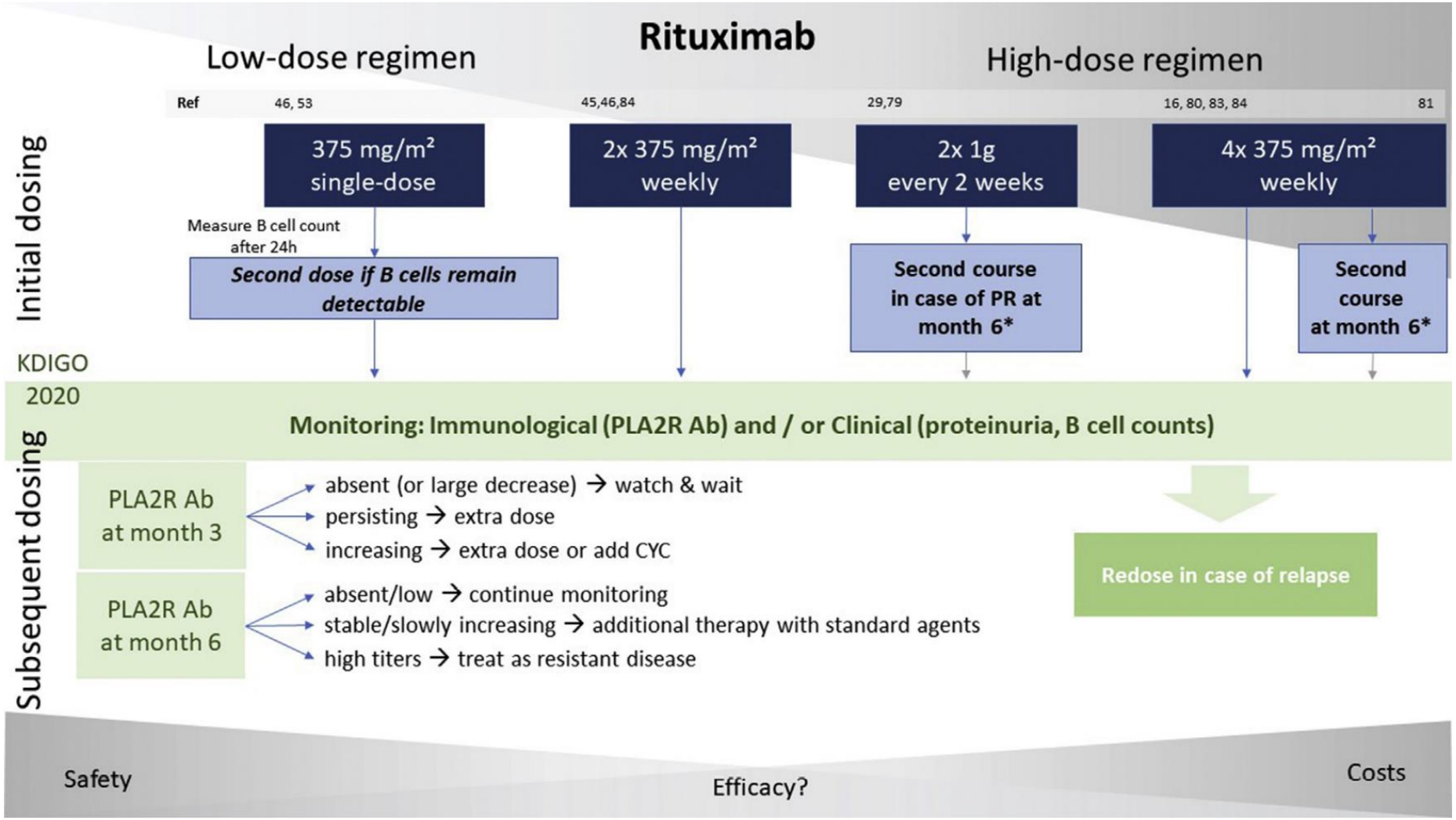
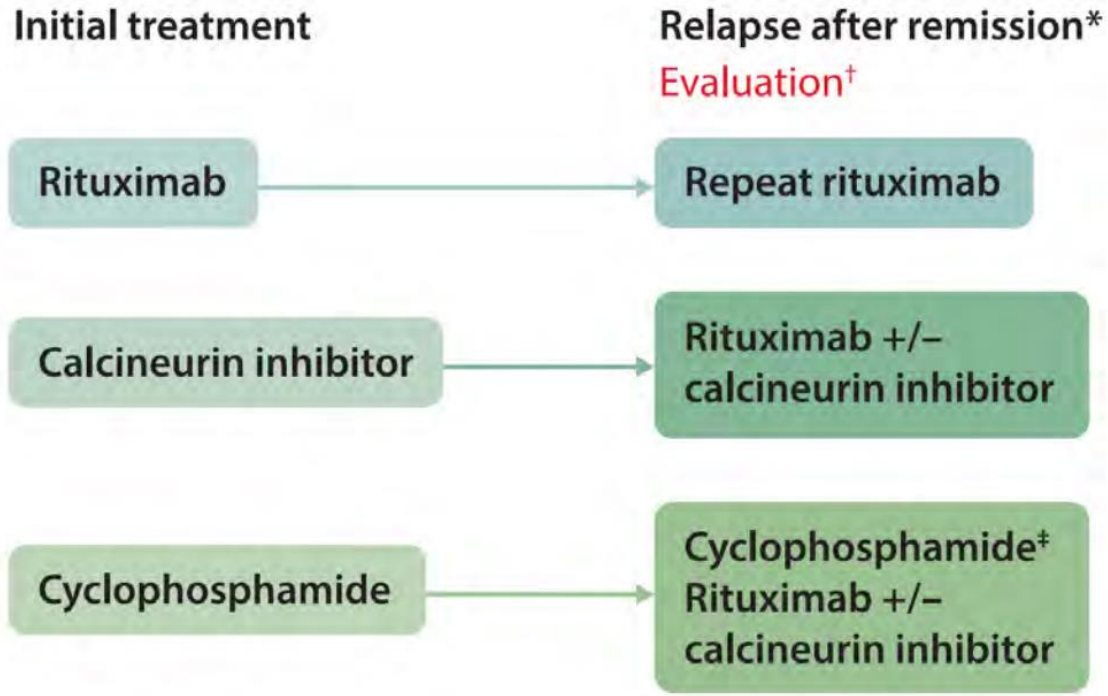


Figure 1. Overview of different dosing regimens used in clinical trials (blue boxes) and a potential algorithm for subsequent dosing as recommended by current Kidney Disease : Improving Global Outcomes guidelines (green boxes).
CYC, cyclophosphamide; PLA2R Ab, M-type phospholipase A2 receptor antibody; PR, partial remission.
* In « high-dose regimens » using a second course of the initial rituximab dosing after 6 months, KDIGO recommendations for subsequent dosing in the first 6 months are not applicable (gray arrows). Nonetheless, subsequent dosing may be guided similarly thereafter.

Figure MN6. Management of initial relapse after therapy



*The definition of relapse is variable. Some authors define relapse after remission as an increase in proteinuria >3.5 g/day in patients who developed a partial or complete remission. We suggest that the course of serum albumin and PCR should be used in the evaluation. If PCR decreased to values between 2 and 3.5 g/day without an increase of serum albumin to normal, the subsequent rise in PCR should be considered resistant disease rather than relapse after remission. In patients with a partial remission (characterized by normalization of serum albumin), a relapse should be defined by an increase of proteinuria paralleled by a decrease in serum albumin levels.

†Immunological monitoring is of particularly great value in these situations. If, in the period of "clinical remission", PLA2Rab were still positive, this would be evidence for resistant disease. Therefore, in patients with positive PLA2Rab, it is advised to evaluate PLA2Rab at the time of remission and relapse. The course of PLA2Rab should precede the clinical course. In patients with very early relapse, it is important to consider reasons for the failure of the previous therapy (e.g., compliance, low drug levels, insufficient B cell depletion, presence of anti-rituximab antibodies).

‡Cyclophosphamide can be repeated; however, physicians must take into account the maximal tolerable dose: the cumulative dose should not exceed 10 g if preservation of fertility is required. The cumulative dose should not exceed 25 g to limit risk of malignancies.

Details of commonly used treatment regimens are shown in Table MN2.

• Conclusion:

- As recommended by the currently updated KDIGO guideline for glomerular diseases, rituximab is a promising new first-line treatment option for patients with primary MN.

- Although a classical cyclical therapy consisting of alkylating agents and corticosteroids is still recommended for a certain subset of patients at very high risk for progressive kidney disease, rituximab might be the treatment of choice for most patients at moderate and high risk.
- Progressive loss of kidney function with an estimated glomerular filtration rate (eGFR) .

- Consequently, these patients are rarely included in clinical trials, and risk-benefit assessment usually results in withholding immunosuppressants.

- Considering the lack of data, it remains unknown which patients with reduced kidney function may benefit from immunosuppression
- Nonetheless, important questions, such as long-term efficacy and safety, the optimal dosing regimen, and application-timing or strategies for patients with advanced chronic kidney disease or MN refractory to rituximab still remain unanswered. For now, it appears reasonable that treatment with rituximab is adapted individually to each patient's disease course.

- Monitoring disease activity by serial measurement of PLA2R Ab levels may allow such tailored long-term treatment and low-dose protocols with titrated rituximab applications according to B-cell counts and PLA2R Ab levels may be appropriate in selected scenarios to reduce side effects and costs.

- Although a sequential induction strategy of tacrolimus followed by a rituximab single-dose appears inferior to a cyclical therapy of steroids and alkylating agents, direct comparison between rituximab alone and the cyclical therapy is still based on contraposition of rituximab with historical cohorts and thus afflicted by severe limitations. Results by the ongoing RI-CYCLO trial may provide answers to this critical question helping to find the optimal treatment modality for selected patients. Meanwhile RITERM, a multicenter, international retrospective study, will address several central issues in a large cohort.

Rituximab in AAV

- Relapsing nature of AAV ..
- The substantial toxicity associated with cumulative cyclophosphamide use,

- In April 2011, rituximab was approved by the US FDA as an alternative to cyclophosphamide in combination with glucocorticoids for treatment of severe GPA/MPA.

- Two randomized controlled trials, RAVE and RITUXVAS, evaluated the use of rituximab, …

- In the RAVE trial, patients with both new and relapsing GPA/MPA were enrolled (Scr < 4 mg/dL).

- The RITUXVAS trial enrolled only patients with newly diagnosed GPA/MPA with more severe kidney disease, including patients requiring dialysis.

- Rituximab is the preferred treatment for patients with relapsing disease, refractory disease, and those with contraindications to cyclophosphamide.

- In subgroup analysis, the RAVE trial demonstrated that rituximab was superior to cyclophosphamide for remission induction in patients with PR3- positive ANCA.

- Rituximab dosed at 1,000 mg every 2 weeks for 2 doses, similar to the dosing in rheumatoid arthritis, has been demonstrated to produce reliable B-cell depletion with comparable outcomes at reduced cost.

- When rituximab is given to patients undergoing plasmapheresis, it is important to remember that there is considerable removal of rituximab by plasmapheresis.

- There are no guidelines concerning the optimal timing of rituximab administration after plasma exchange.

- In the PEXIVAS trial, plasma exchange was withheld for 48 hours after the initial rituximab do

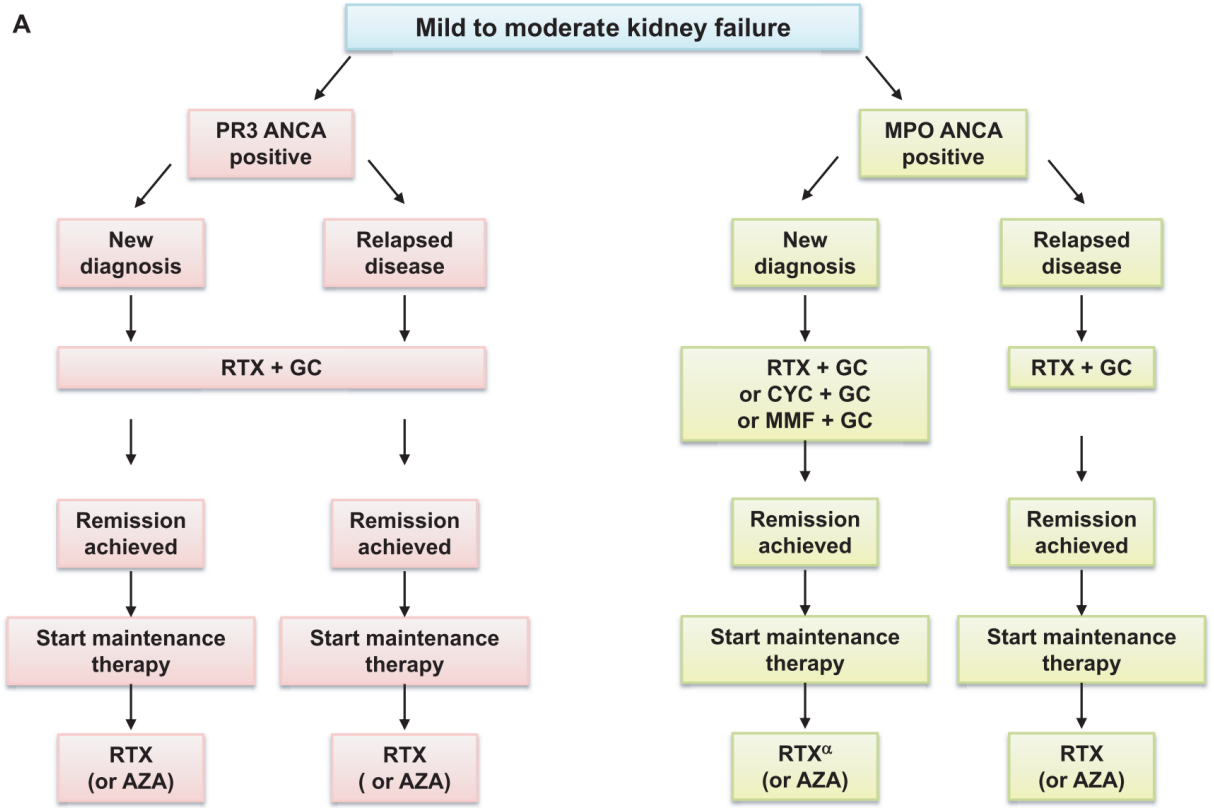


Figure 4. (A, B) Proposed treatment algorithm for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. [α]Maintenance therapy should be individualized according to the risk for relapse. Patients with myeloperoxidase (MPO)-ANCA have a lower relapse risk and a shorter duration (18-24 months) of therapy may be appropriate after initial presentation. [β]Data are limited in patients with advanced kidney failure at presentation; the authors prefer a cyclophosphamide (CYC)-based regimen, such as that used in the RITUXVAS trial in this setting. [γ]Patients who have reached end-stage kidney disease and have no extrarenal manifestations may not require maintenance immunosuppression. Abbreviations: AZA, azathioprine; GC, glucocorticoids; MMF, mycophenolate mofetil; PR3, proteinase 3; RTX, rituximab.

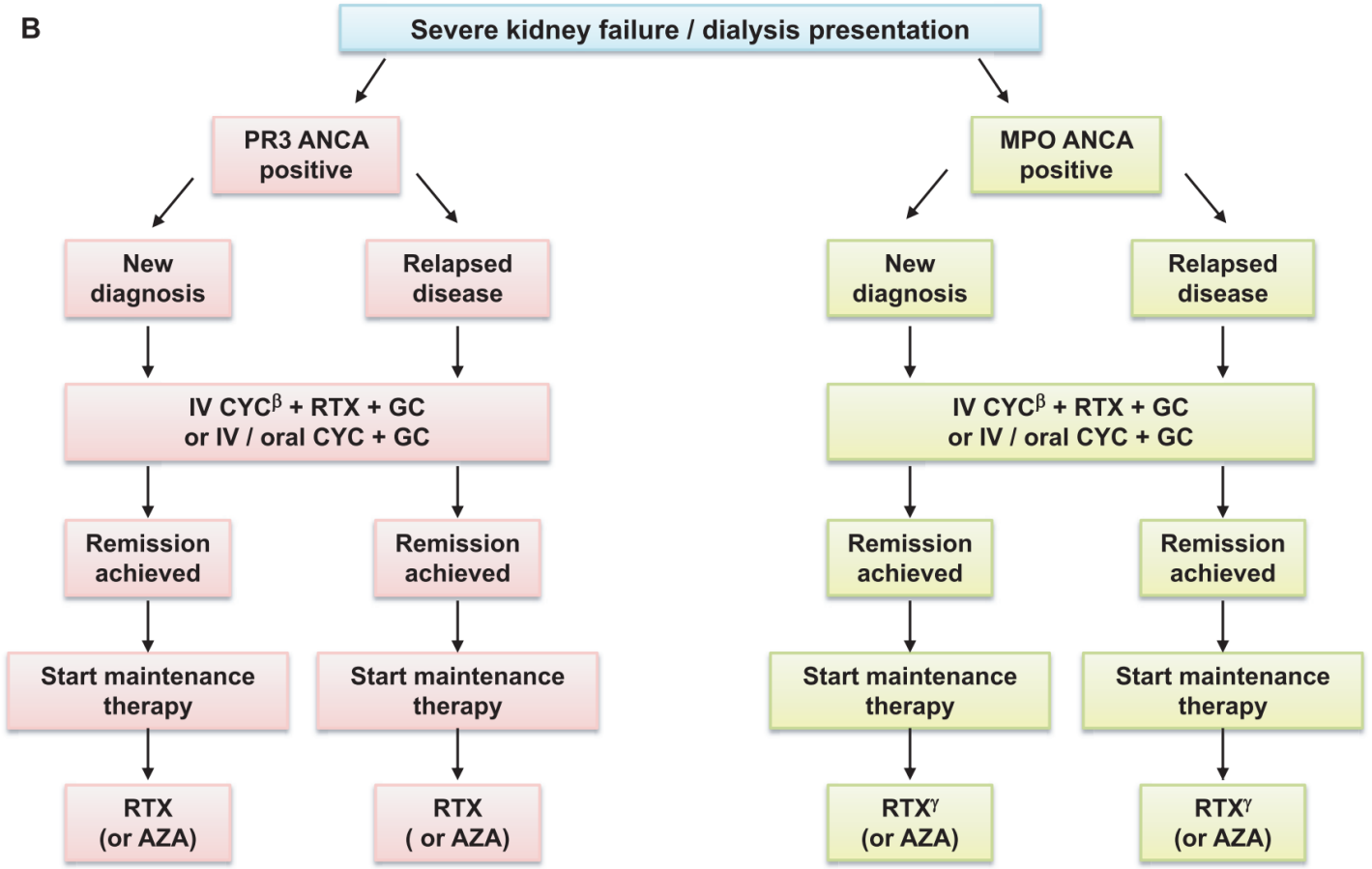


Figure 4. (A, B) Proposed treatment algorithm for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. [α]Maintenance therapy should be individualized according to the risk for relapse. Patients with myeloperoxidase (MPO)-ANCA have a lower relapse risk and a shorter duration (18-24 months) of therapy may be appropriate after initial presentation. [β]Data are limited in patients with advanced kidney failure at presentation; the authors prefer a cyclophosphamide (CYC)-based regimen, such as that used in the RITUXVAS trial in this setting. [γ]Patients who have reached end-stage kidney disease and have no extrarenal manifestations may not require maintenance immunosuppression. Abbreviations: AZA, azathioprine; GC, glucocorticoids; MMF, mycophenolate mofetil; PR3, proteinase 3; RTX, rituximab.

• Maintenance of Remission

- Once remission has been induced, continued lower-level immune suppression is needed for most patients to prevent relapse, which usually entails low-dose glucocorticoids plus an additional immunomodulatory therapy such as azathioprine, rituximab, or mycophenolate mofetil (MMF) for 12–18 months.
- Patients with PR3-ANCA or GPA are more likely to relapse than patients with MPO-ANCA, .. .

- Maintenance therapy may be for a shorter interval or not required for patients at low risk for relapse, such as patients with MPO-ANCA who have complete remission and are MPO-ANCA negative.
- More prolonged maintenance may be appropriate for patients with increased risk for relapse, such as PR3-ANCA positivity, prior recurrence, and pulmonary involvement.

- Sustained use of cyclophosphamide is not recommended because of toxicity.
- A randomized controlled trial comparing cyclophosphamide for 12 months with maintenance therapy with azathioprine once complete remission is attained demonstrated no difference in outcome including relapse rate (48,49).

- Compared with azathioprine, maintenance therapy with MMF was associated with a significantly higher rate of relapse .
- Nevertheless, MMF remains an option for maintenance therapy in patients who are intolerant or allergic to azathioprine.
- Methotrexate may be useful in maintaining remission in patients with mild disease and no renal impairment

- **Rituximab is another option for maintenance of remission.**

- The Maintenance of Remission using Rituximab in Systemic ANCA-associated vasculitis trial (**MAINRITSAN**) **compared rituximab (500 mg iv every 6 months) to azathioprine for remission maintenance in patients with MPA, RLV, and GPA in complete remission after induction treatment with a cyclophosphamide and glucocorticoid regimen (50).**

Rituximab was better than azathioprine for preventing relapse, inc**luding renal relapse**.

- The **optimum duration** **of maintenance therapy** depends on multiple factors.
- Ending too soon increases the risk of relapse.
- Patients with PR3-ANCA (versus MPO-ANCA),
- lung, or upper respiratory tract vasculitis have a higher risk for relapse that warrants longer maintenance therapy.
-
- However, in a randomized controlled trial of patients with PR3-ANCA disease who remained ANCA-positive at the time of stable remission, extending the duration of maintenance therapy with azathioprine from 1 year (followed by taper) to 4 years (followed by taper) was not associated with a significant difference in relapse-free survival at 4 years (54). The result of this study should not be extrapolated to other agents, and the optimal duration of maintenance therapy with rituximab has not been formally evaluated.
- Conversely, patients with none of the risk factors of relapse may not need an extended duration of maintenance therapy.

- Relapse Treatment and Other Challenges

- Some patients with ANCA disease are refractory to induction of remission. In some studies, patients with PR3- ANCA are more likely to have refractory disease .

- Options for the treatment of refractory disease include the addition of plasmapheresis, or the addition of rituximab to a cyclophosphamide-based regime, or vice versa.

- In patients with very severe disease at the time of diagnosis, such as dialysis-dependent kidney disease with extensive glomerular scaring on renal biopsy, a decision to treat with toxic immunosuppressive therapy can be difficult.

- However, patients with ANCA GN with severe kidney failure at the initiation of therapy have a low but not negligible response to treatment.

Combination treatment with rituximab, low-dose cyclophosphamide and plasma exchange for severe antineutrophil cytoplasmic antibody-associated vasculitis

Kavita Gulati[1,2,3], Helena Edwards[1,3], Maria Prendecki[1,2], Thomas D. Cairns[1], Marie Condon[1], Jack Galliford[1], Megan Griffith[1,2], Jeremy B. Levy[1,2], Frederick W.K. Tam[1,2], Anisha Tanna[1], Charles D. Pusey[1,2] and Stephen P. McAdoo[1,2]

[1]Vasculitis Clinic, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; and [2]Centre for Inflammatory Disease, Immunology & Inflammation, Imperial College London, London, UK

severe disease as presentation with DAH and/or severe kidney injury (i.e., serum creatinine >500 mmol/L [5.7 mg/dl] or the need for renal replacement therapy [RRT]) before commencing treatment.

Table 1 | Treatment protocol

Variable	Agent	Dose
Plasma exchange		
Commencing day 0 or 36 h after cytotoxic therapy	Against 4.5% or 5% HAS (or FFP if risk of bleeding)	Daily exchange ×7; 60 ml/kg (max, 4 L)
Cytotoxic		
Day 0	I.v. cyclophosphamide	10 mg/kg (max, 750 mg)
Day 7	I.v. rituximab[a]	1 g
Week 2	I.v. cyclophosphamide	10 mg/kg (max, 750 mg)
	I.v. rituximab	1 g
Weeks 4, 6, 8, and 10	I.v. cyclophosphamide	500 mg
Glucocorticoid taper		
Week 1	Oral prednisolone	1 mg/kg per day (max, 60 mg/d)[b]
Week 2	25% Reduction	45 mg/d
Week 3	33% Reduction	30 mg/d
Week 4	33% Reduction	20 mg/d
Week 6	25% Reduction	15 mg/d
Week 12		12.5 mg/d
Week 20		10 mg/d
Maintenance		
From week 12	Azathioprine	2 mg/kg per day
	MMF	0.5–1 g daily if intolerant
Adjuvant therapy		
PJP prophylaxis	Cotrimoxazole or pentamidine nebulizers	480 mg/d
		300 mg/mo (if intolerant)
Peptic ulcer prophylaxis	Proton-pump inhibitor	
Bone prophylaxis	Vitamin D and calcium supplementation	
Latent TB treatment (in those from high-risk areas)	Isoniazid and pyridoxine	150 mg/d
		50 mg/wk

FFP, fresh-frozen plasma; HAS, human albumin solution; max, maximum; MMF, mycophenolate mofetil; PJP, *Pneumocystis jirovecii* pneumonia; TB, tuberculosis.
[a]Rituximab was initiated at completion of plasma exchange.
[b]If received i.v. glucocorticoid before referral, then starting dose may be reduced to 0.5 mg/kg per day.

Table 2 | Patient demographics, comorbidities, and baseline disease features

Variable	All	MPO-ANCA	PR3-ANCA
Demographics			
Patients, n (%)	64	33 (52)	31 (48)
Male/female ratio (% male)	39:25 (61)	22:11 (67)	17:14 (55)
Age, yr, median (range)	66 (22–84)	69 (27–84)	65 (22–78)
Preexisting comorbidities, n (%)			
Lung disease[a]	20 (31)	12 (30)	8 (26)
Diabetes mellitus	14 (22)	7 (21)	7 (23)
Cardiovascular disease[b]	13 (20)	8 (24)	5 (16)
Prior malignancy	8 (13)	4 (12)	4 (13)
Chronic kidney disease[c]	8 (13)	4 (12)	4 (13)
Disease status at presentation			
De novo presentation, n (%)	58 (91)	32 (97)	26 (84)
BVAS	19 (16–23)	18 (14–21)	21 (19–25)
Creatinine, µmol/L	558 (390–617)	544 (473–624)	560 (292–629)
eGFR, ml/min	9 (7–13)	8 (7–12)	9 (7–16)
CRP, mg/L	108 (50–164)	77 (29–153)	120 (61–184)

ANCA, anti–neutrophil cytoplasm antibody; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MPO, myeloperoxidase; PR3, proteinase 3.
[a]Lung disease included asthma, chronic obstructive airway disease, pulmonary fibrosis, and bronchiectasis.
[b]Cardiovascular disease included cardiac disease, peripheral disease, and cerebrovascular disease.
[c]Chronic kidney disease included diabetic nephropathy, renovascular disease, and obstructive uropathy
Values reported as proportions or median (interquartile range), unless otherwise stated.

Table 4 | Deaths and adverse events

Deaths in first 3 years

Time point, mo	Age, yr	Cause of death
1	77	Vasculitis damage: frail, dialysis dependent, with no response to initial treatment; transitioned early to supportive care
5	81	Dialysis catheter-associated sepsis
5	59	Sepsis
6	72	Presumed metastatic lung carcinoma
12	63	Dialysis catheter-associated sepsis
13	76	Vasculitis damage: cerebral vasculitis with significant residual disability; transitioned to supportive care
17	55	Vasculitis relapse: ischemic mesenteric colitis with perforated bowel and invasive group A streptococcal infection
26	60	COVID-19 pneumonitis
27	86	Sepsis secondary to pneumonia

Adverse events during entire study follow-up

Grade III infections	n (%)
• None	40 (63)
• 1 Infection	9 (14)
• ≥2 Infections	15 (23)
• Zoster	4 (6)
• *Pneumocystis jirovecii*	1 (2)
Hypogammaglobulinemia	11 (17)
Malignancy	5 (8)
New-onset diabetes	4 (6)

COVID-19, coronavirus disease 2019.

All patients received a minimum of seven plasma exchanges, and the median cumulative doses of rituximab, cyclophosphamide, and glucocorticoid were 2, 3, and 2.6 g, respectively, at six months. A total of 94% of patients had achieved disease remission (version 3 Birmingham Vasculitis Activity Score of 0) at this time point, and 67% of patients who required dialysis recovered independent kidney function.

During **long-term follow-up** (median duration **46 months**), overall patient survival was 85%, and 69% of patients remained free from end-stage kidney disease, which compares favorably to a historic cohort with severe disease treated with a conventional induction regimen.

Combination treatment was associated with prolonged B cell depletion and low rates of relapse; 87% of patients were in continuous remission at month 36.

The serious infection rate during total follow-up was 0.28 infections/patient/year, suggesting that combination treatment is not associated with an enduring risk of infection. Thus, we suggest that combination immunosuppressive therapy may permit glucocorticoid avoidance and **provide rapid and prolonged disease control in patients with severe ANCA-associated vasculitis.**

IgA Nephropathy: Core Curriculum 2021

Prapa Pattrapornpisut, Carmen Avila-Casado, and Heather N. Reich

- Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide.

- Although proteinuria is attenuated by the use of corticosteroids, the long-term benefits have been questioned, and the use of corticosteroids is associated with severe adverse effects, notably infection.
- in patients with RPGN, intravenous methylprednisolone followed by a combination of either oral or intravenous cyclophosphamide and corticosteroids, as in ANCA associated vasculitis, is recommended; however, there are no randomized studies to support these recommendations.
- there are no clinical trial data to support the use of rituximab in RPGN due to IgAN.

- Anecdotal successful use of rituximab has primarily been reported in IgAN presenting with IgA vasculitis; a lack of improvement in proteinuria or kidney function in patients with IgAN without RPGN suggests a lack of a role for rituximab in this context.

- This is an area where **multicenter randomized clinical trials are urgently needed**

nature reviews nephrology

Explore content | About the journal | Publish with us | Subscribe

nature > nature reviews nephrology > news & views > article

Published: 28 December 2016

Glomerular disease

Rituximab therapy for IgA nephropathy

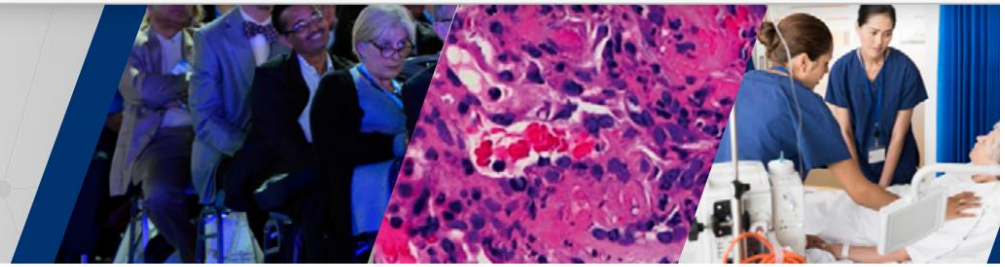
Jürgen Floege

Nature Reviews Nephrology **13**, 138–140 (2017) | Cite this article

1603 Accesses | **3** Citations | **2** Altmetric | Metrics

As IgA nephropathy (IgAN) is considered to result in part from autoimmune processes, B-cell depletion using rituximab might be a plausible therapy. However, a small randomized, controlled trial in patients at risk of progressive IgAN reports that this therapy failed to reduce proteinuria over 1 year and was associated with more adverse events per patient.

Refers to Lafayette R. A. *et al.* A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. *J. Am. Soc. Nephrol.*



Management of Adult Minimal Change Disease

Stephen M. Korbet and William L. Whittier

CJASN 14: 911–913, 2019. doi: https://doi.org/10.2215/CJN.01920219

Recent studies with rituximab in adults with frequently relapsing/steroid-dependent minimal change disease who failed treatment with other agents have shown encouraging results .

Drug Design, Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Consolidation Treatment and Long-Term Prognosis of Rituximab in Minimal Change Disease and Focal Segmental Glomerular Sclerosis

Li Lin[1]
Weiming Wang[1]
YiFan Wu[2]
JingYuan Xie[1]
Xiao Li[1]
XiaoXia Pan[1]
Wen Zhang[1]
Jing Xu[1]
YiKai Cai[1]
Hong Ren[1]
Nan Chen[1]

[1]Department of Nephrology, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, People's Republic of China; [2]Biomedical and Health Informatics, University of Washington, Seattle, WA, USA

Purpose: There is currently a lack of studies investigating long-term prognosis and the necessity of further rituximab (RTX) consolidation treatment for minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). The aim of this study was to evaluate the efficacy of RTX for these diseases and to investigate whether a consolidation treatment can lower risks of relapse and reinforce long-term remission.

Patients and Methods: A retrospective study was conducted. The relapse and remission of 70 patients treated with 1 course of RTX treatment (4 infusions of 375 mg/m2) over a median follow-up time of 27 months (12–60 months) were analyzed. The rates of patients that were able to achieve non-relapse for a duration of 24 months between RTX consolidation therapy and non-consolidation therapy were compared.

Results: There were 67 cases (95.71%) of remission and 3 cases (4.29%) of non-remission. The average number of relapses decreased from 3.7±2.5 times before the treatment to 0.8 ±1.8 times after treatment (P <0.001). The average avannual number of relapses decreased from 1.3±1.2 times/year to 0.2±0.3 times/year (P <0.001). The results from the Cox proportional-hazards model showed that the risk of relapse in patients who received RTX non-consolidation treatment was significantly higher than those with consolidation treatment (odds ratios (OR) 20.9, 95% confidence intervals (CI) OR 5.7–75.7, p<0.001). The 24-month relapse-free rate was also significantly higher in patients with consolidation therapy compared with non-consolidation therapy (86.36% vs 25%, p<0.001). No adverse events were recorded.

Conclusion: RTX is highly effective in treating MCD and FSGS, and RTX consolidation therapy may be recommended to reinforce long-term remissions.

Keywords: RTX, MCD, FSGS, consolidation, therapeutic effect

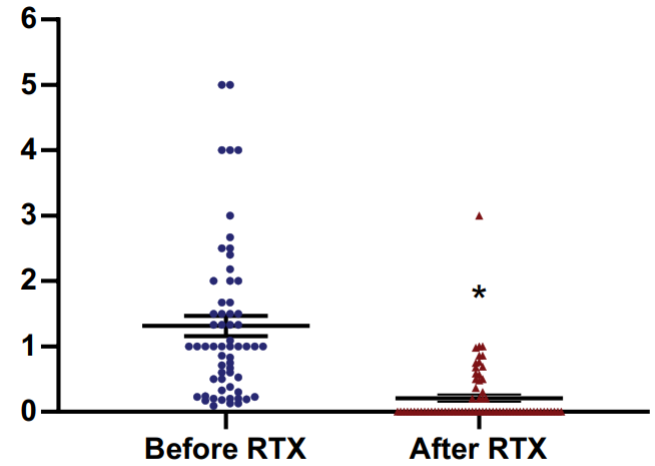
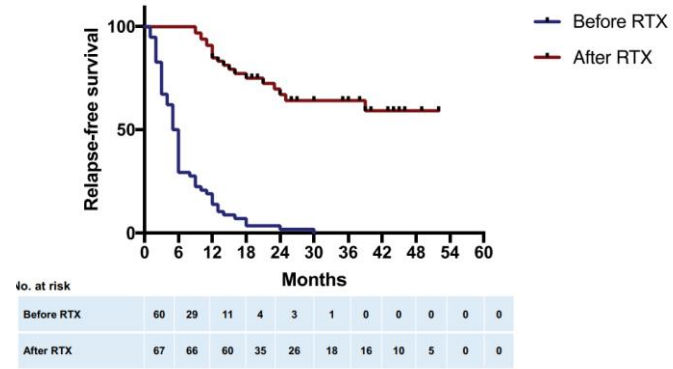


Figure 1 The number of relapses ±SD per year before and after rituximab treatment (*P<0.05).



survival before and after RTX therapy in the overall cohort.
e survival rate was significantly higher for patients after taking RTX therapy compared to before (log-rank p<0.001). This graph d
e of patients to start relapsing. Both lines describe the same group of patients, and the red line follows the blue line in terms of
TX (blue line), all patients relapsed before 30 months, while after using RTX (red line), more than 50% did not see relapse by
alysis.

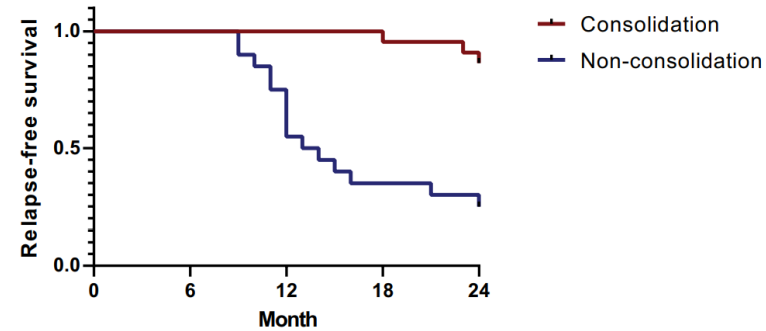


Figure 3 24-month relapse-free survival in the consolidation and non-consolidation groups.
Notes: The 24-month relapse-free survival rate was significantly higher in patients with consolidation compared to non-consolidation (log-rank <0.001). Only patients who achieved PR or CR and completed 24-month follow-up are included in this graph. The induction RTX was given at the baseline for both groups. Beginning at the 6th month, consolidation treatments were administered for the consolidation group, while non-consolidation groups did not receive further treatment.

Autoimmunity Reviews 19 (2020) 102671

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Rituximab in adult minimal change disease and focal segmental glomerulosclerosis - What is known and what is still unknown?

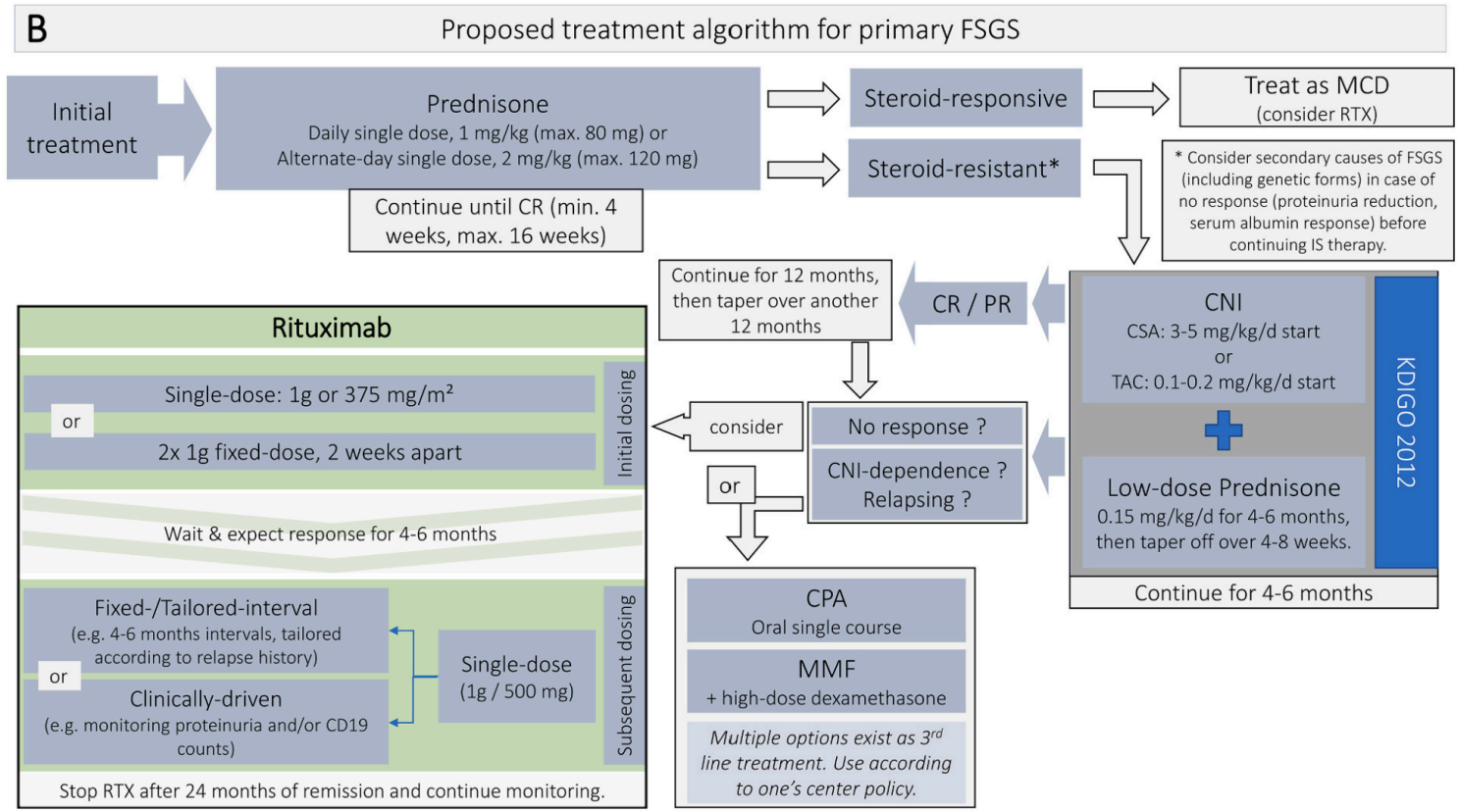


Fig. 4. Proposed algorithm for the application of rituximab in primary focal segmental glomerulosclerosis.
FSGS, focal segmental glomerulosclerosis; CR, complete remission; MCD, minimal change disease; RTX, rituximab; IS, immunosuppressive; CNI, calcineurin inhibitors; CSA, cyclosporin A; TAC, tacrolimus; PR, partial remission; CPA, cyclophosphamide; MMF, mycophenolate mofetil; CD, cluster of differentiation.

KI REPORTS
KIReports.org
CLINICAL RESEARCH

Efficacy of Rituximab in Treatment-Resistant Focal Segmental Glomerulosclerosis With Elevated Soluble Urokinase-Type Plasminogen Activator Receptor and Activation of Podocyte β3 Integrin

Michelle A. Hladunewich[1,7], Dan Cattran[2,7], Sanjeev M. Sethi[3], Salim S. Hayek[4], Jing Li[5], Changli Wei[5], Sarah I. Mullin[1], Heather N. Reich[2], Jochen Reiser[5,7] and Fernando C. Fervenza[6,7]

[1]Division of Nephrology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; [2]Division of Nephrology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada; [3]Department of Pathology, Mayo Clinic, Rochester, Minnesota, USA; [4]Division of Cardiology, Department of Medicine, University of Michigan, Ann Arbor, Minnesota, USA; [5]Division of Nephrology, Department of Medicine, Rush University Medical Center, Chicago, Illinois, USA; and [6]Division of Nephrology, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

Introduction: Severe, nonresponsive, primary focal segmental glomerular sclerosis (FSGS) can progress to end-stage kidney disease (ESKD) in <5 years. Soluble urokinase-type plasminogen activator receptor (suPAR) may contribute to podocyte effacement by activating podocyte β3 integrin. It has been reported as a potential permeability factor and biomarker for primary FSGS. Rituximab was found to have efficacy in case reports and small series. Whether rituximab is efficacious in patients with treatment-resistant FSGS in the context of high suPAR levels and evidence of podocyte B3 integrin activation remains unknown.

Methods: In this nonblinded, open-label pilot study, the safety and efficacy of rituximab were evaluated in treatment-resistant adult patients with primary FSGS and a suPAR level > 3500 pg/ml with evidence of β3 integrin activation. Rituximab (1 g) was given on days 1 and 15. The primary outcome was proteinuria at 12 months.

Results: Only 13 of 38 screened patients qualified for the study, of whom 9 consented to participate. The baseline proteinuria and glomerular filtration rate (GFR) levels were 7.70 ± 4.61 g/d and 67 ± 38 ml/min, respectively. A transient response at 6 months was noted in 2 patients without a parallel change in suPAR level. At 12 months, there was no statistically significant improvement in proteinuria level with all participants remaining nephrotic (7.27 ± 7.30 g/d). GFR level marginally declined to 60 ± 38 ml/min with one patient progressing to ESKD. There were 2 serious infections, an infusion-related reaction and leucopenia attributed to rituximab.

Conclusion: Rituximab was ineffective when administered to adult patients with treatment-resistant primary FSGS with a high suPAR and evidence of podocyte activation.

Kidney Int Rep (2022) **7**, 68–77; https://doi.org/10.1016/j.ekir.2021.10.017
KEYWORDS: focal segmental glomerulosclerosis (FSGS); nephrotic syndrome; rituximab; soluble urokinase-type plasminogen activator receptor (suPAR); treatment resistance

review www.kidney-international.org

The lupus nephritis management renaissance

Juan M. Mejia-Vilet[1], Ana Malvar[2], Arnon Arazi[3] and Brad H. Rovin[4]

[1]Department of Nephrology, Instituto Nacional de Ciencas Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico; [2]Department of Nephrology, Hospital Fernandez, Buenos Aires, Argentina; [3]Institute of Molecular Medicine, Feinstein Institutes for Medical Research, Manhasset, New York, USA; and [4]Department of Medicine and Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

- On the basis of phase 3 data, belimumab and voclosporin received approval by the US FDA for LN treatment, and obinutuzumab is currently undergoing testing in a phase 3 RCT.

- The excitement of these outcomes has now given way to questions on how to best use these newly approved regimens.

- Voclosporin is a calcineurin inhibitor (CNI) modified from the cyclosporine backbone that is more potent than cyclosporine, seems to cause less hypertension and hyperlipidemia than cyclosporine, seems to cause less diabetes than tacrolimus, and, at least in experimental animals, does not cause CNI nephrotoxicity.
- However, voclosporin has not been compared directly with cyclosporine or tacrolimus for the treatment of LN, so no conclusions can be drawn regarding superior safety or efficacy.

Hindawi
BioMed Research International
Volume 2017, Article ID 2180508, 7 pages
https://doi.org/10.1155/2017/2180508

Review Article

Rituximab for Treatment of Membranoproliferative Glomerulonephritis and C3 Glomerulopathies

Michael Rudnicki

Department of Internal Medicine IV–Nephrology and Hypertension, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria

Correspondence should be addressed to Michael Rudnicki; michael.rudnicki@i-med.ac.at

Received 3 March 2017; Accepted 20 April 2017; Published 9 May 2017

- Data on the use of rituximab in MPGN, C3GN, and DDD are limited to case reports and retrospective case series.

- Patients with immunoglobulin-associated and idiopathic MPGN who were treated with rituximab showed partial and complete responses in the majorities of cases.
- However, rituximab was not effective in few cases of C3GN and DDD.
-
- Despite promising results in immunoglobulin-associated and idiopathic MPGN, current evidence on this treatment remains weak, and controlled and prospective data are urgently needed.

THANK YOU