Rituximab in Nephrology

Dr. Firouzeh Moeinzadeh

Assisstant professor of Nephrology

Isfahan Kidney Diseases Research Center/Isfahan University of Medical Sciences

Outlines

- Rituximab in kidney transplantation
- Rituximab in glomerular disease: Membranous glomerulopathy
- FSGS & minimal change disease
- SLE
- ANCA associated vasculitis

Medically necessary indications

- Idiopathic thrombocytopenic purpura
- Autoimmune mucocutaneous blistering diseases
- Wegener's granulomatosis and microscopic polyangiitis (both ANCA-associated vasculitis)
- Autoimmune hemolytic anemia, including chronic cold agglutinin disease
- Rheumatoid arthritis

Not medically necessary

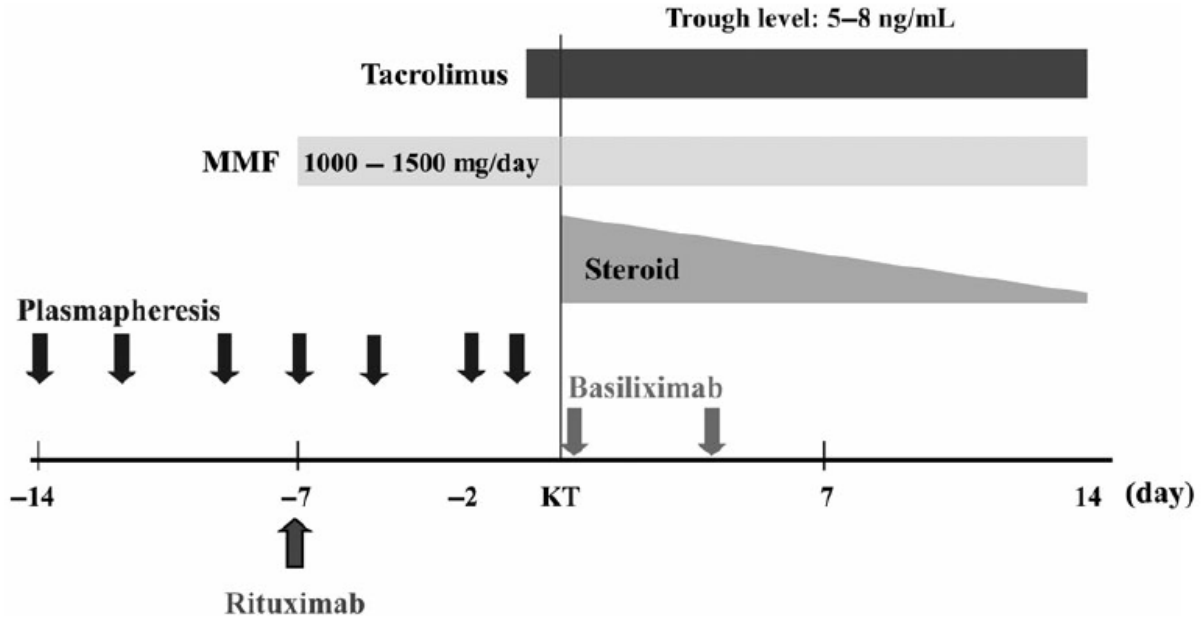
- Anti-GM1 antibody-related neuropathies;
- Post-transplant B-lymphoproliferative disorder;
- Kaposi sarcoma-associated herpes virus-related multicentric Castleman disease;
- Pure red cell aplasia;
- Systemic lupus erythematosus;
- Acquired factor VIII inhibitors;
- Polyneuropathy associated with anti-MAG antibodies;
- Idiopathic membranous nephropathy;
- Chronic graft-versus-host disease;
- Reduction of anti-HLA antibodies in patients awaiting renal transplant;
- Multiple sclerosis
- Neuromyelitis optica;
- Dermatomyositis and polymyositis

Clinical use of rituximab in renal transplantation

- Induction
- Desensitization in antibody incompatible Transplantation
- Treatment of renal allograft rejection .

2013 European Society for Organ Transplantation. Published by Blackwell Publishing Ltd 26 (2013) 563–575

Transplantation induction



Desensitization protocol in ABO-incompatible KT. KT, kidney transplantation; MMF, mycophenolate mofetil.

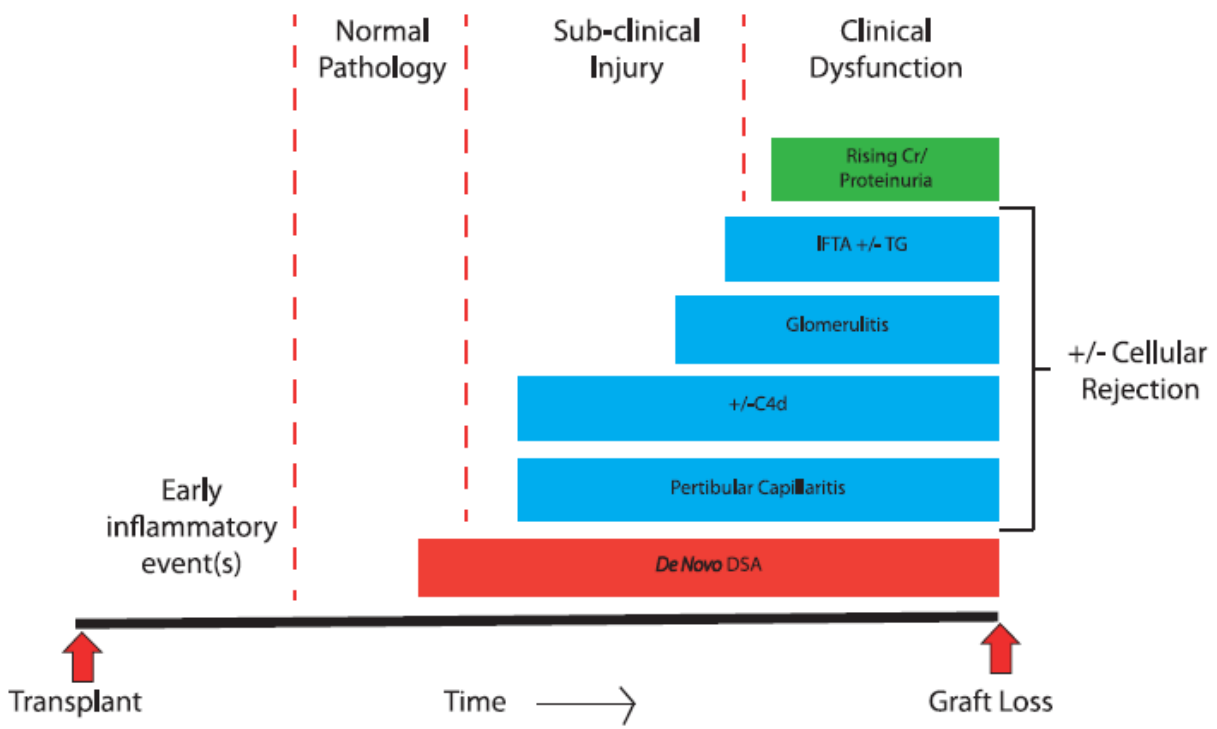
Histologic evidences

Acute AMR

- Microvascular inflammation:
  - Glomerulitis
  - Peritubular capillaritis (PTC)
- Arteritis
- Acute TMA
- Acute tubular injury

Chronic AMR

- Transplant glomerulopathy (TG)
- Multilayering of the PTC basement (requires EM)



Proposed model for patients developing *de novo* DSA as they evolve from transplantation to graft failure.

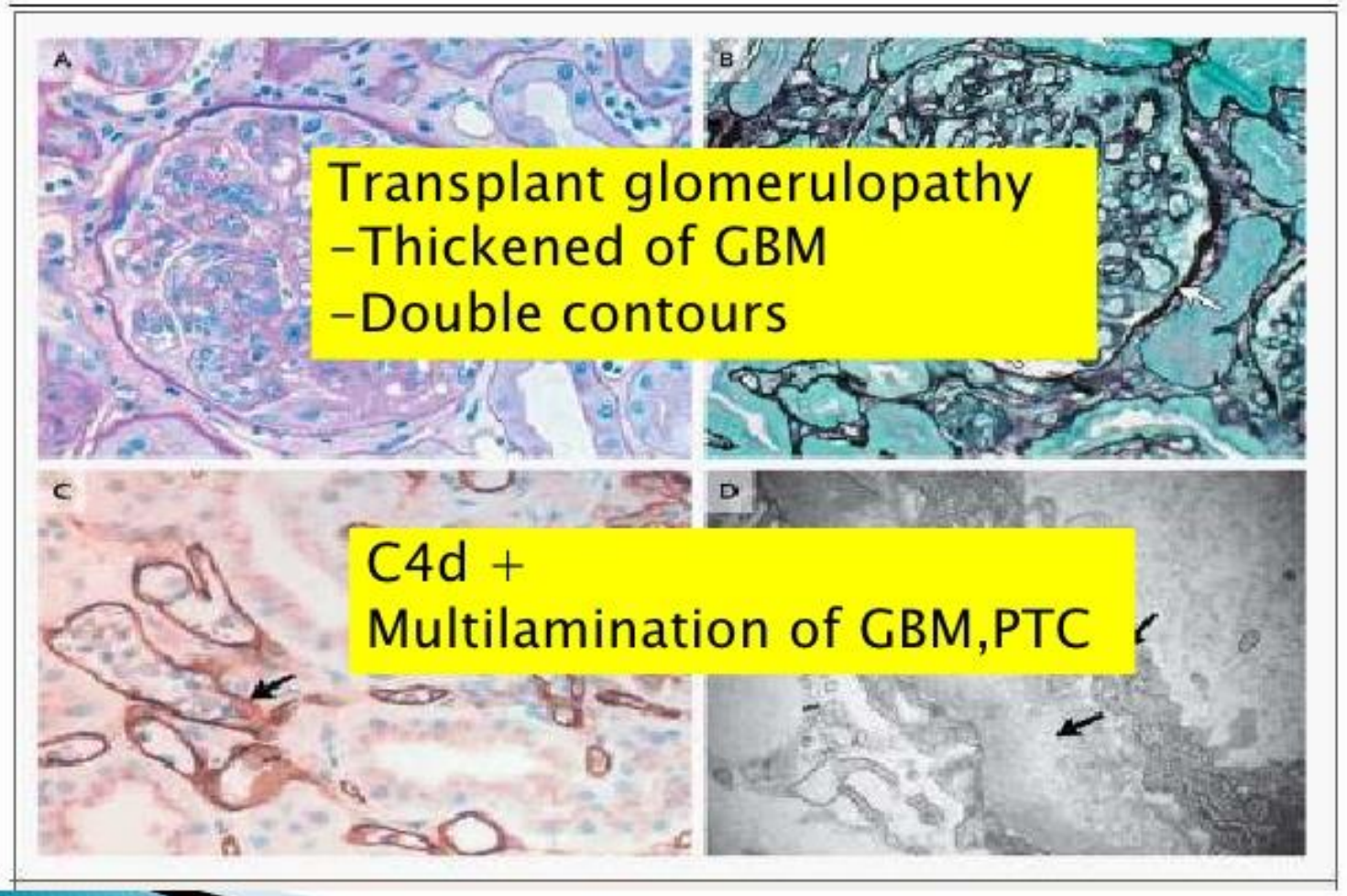
De novo antibody production may cause sub-clinical AMR that is associated with longterm graft dysfunction.

Negative outcomes can take several years to occur after *De novo* antibody production.

The Range of *De novo* DSA

- 62% of liver transplant patients
- 56% of lung transplant patients
- 33% of heart transplant patients
- 27% of multi-visceral transplant patients
- 24% of kidney-pancreas translplant patients

Pathology of Chronic ABMR

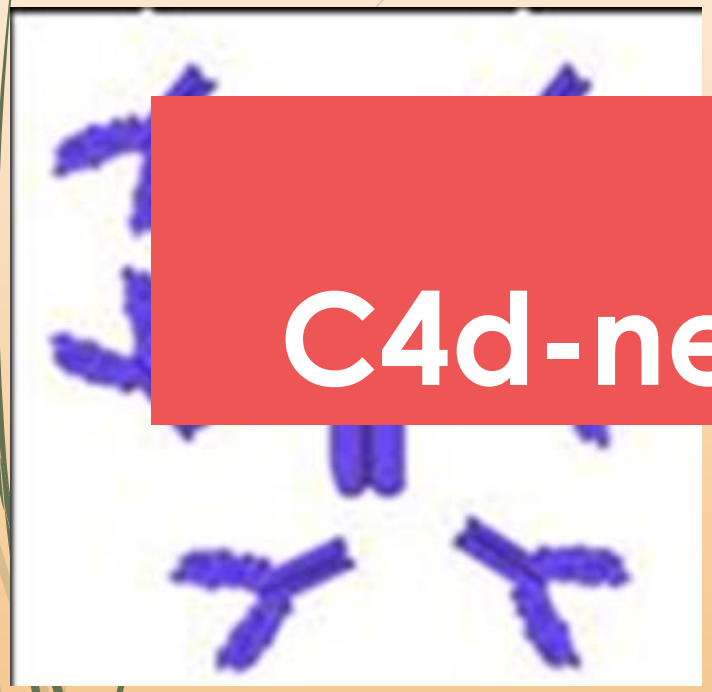


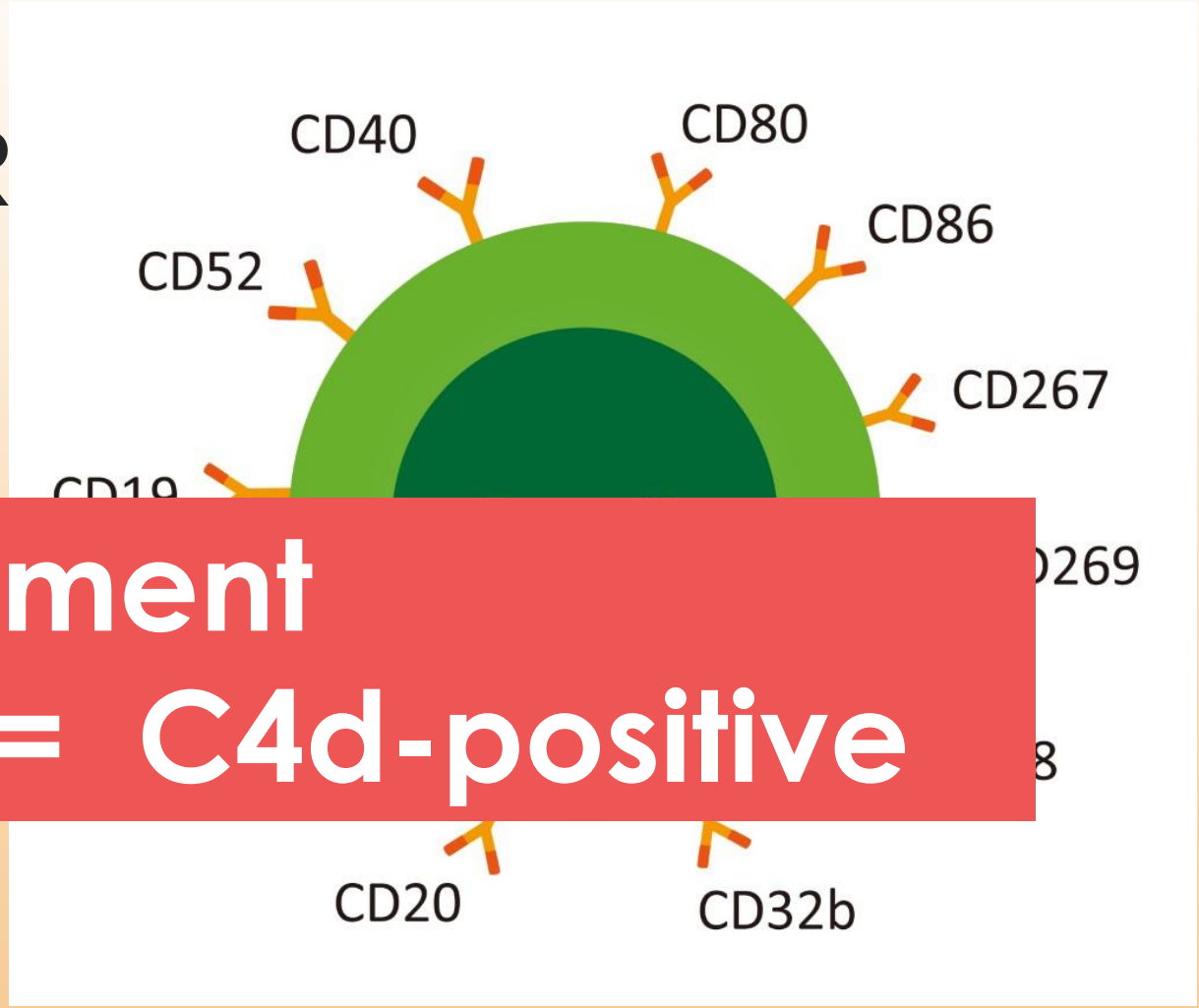
N ENGL J MED 363;15 NEJM.ORG OCTOBER 7, 2010

POOR OUTCOME

- Concurrent acute TCMR
- Microvascular injury
- C4d staining
- Transplant glomerulopathy
- Creatinine of >3 mg/dL
- Proteinuria
- Anti-HLA DSA MFI of >3000
- De-novo DSA

Treatment of ABMR





Treatment
C4d-negative = C4d-positive

remove existing DSAs

Inhibit B cell development, maturation, and activity.

Treatment of ABMR

- The optimal treatment of active ABMR is unclear, and there have been no randomized, controlled trials with adequate statistical power to compare the safety and efficacy of different therapeutic strategies.
- Recommendations for the treatment of ABMR are primarily based upon available, low-quality evidence and are largely consistent with the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines.

The optimal treatment of active ABMR is unclear

Treatment of ABMR

- Methylprednisolone
- IVIG
- Plasma exchange
- Rituximab

Djamali et al

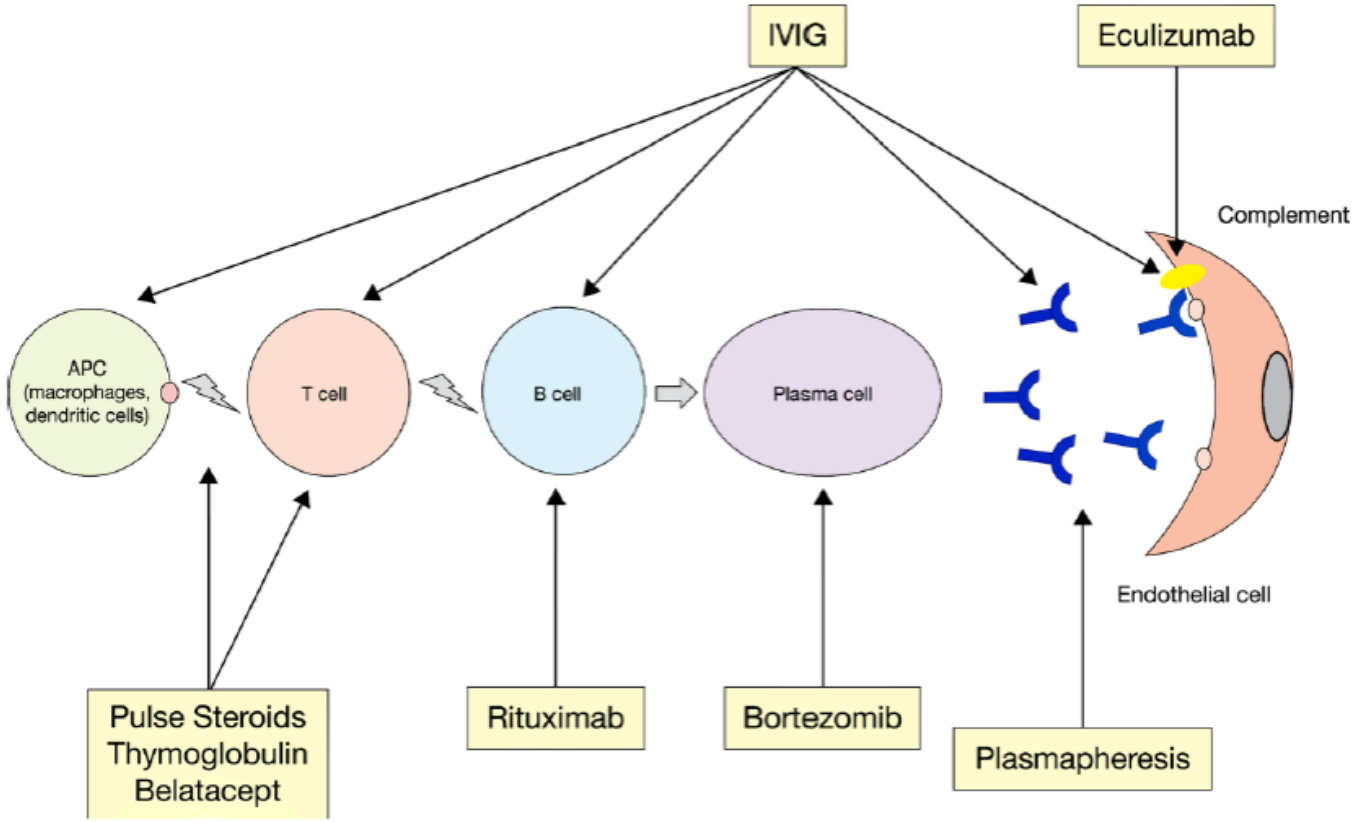


Figure 4: Therapeutic modalities for ABMR. ABMR, antibody-mediated rejection; APC, antigen-presenting cell; IVIG, intravenous immunoglobulins.

ABMR within the first year

- IV methylprednisolone at a dose of 300 to 500 mg daily for three to five days, followed by a rapid oral prednisone taper to the patient's previous maintenance dose of prednisone.
- If there are no concerns for nonadherence, we augment the maintenance prednisone dose.

Plasmaphresis

QD or QOD maximum of 6 sessions

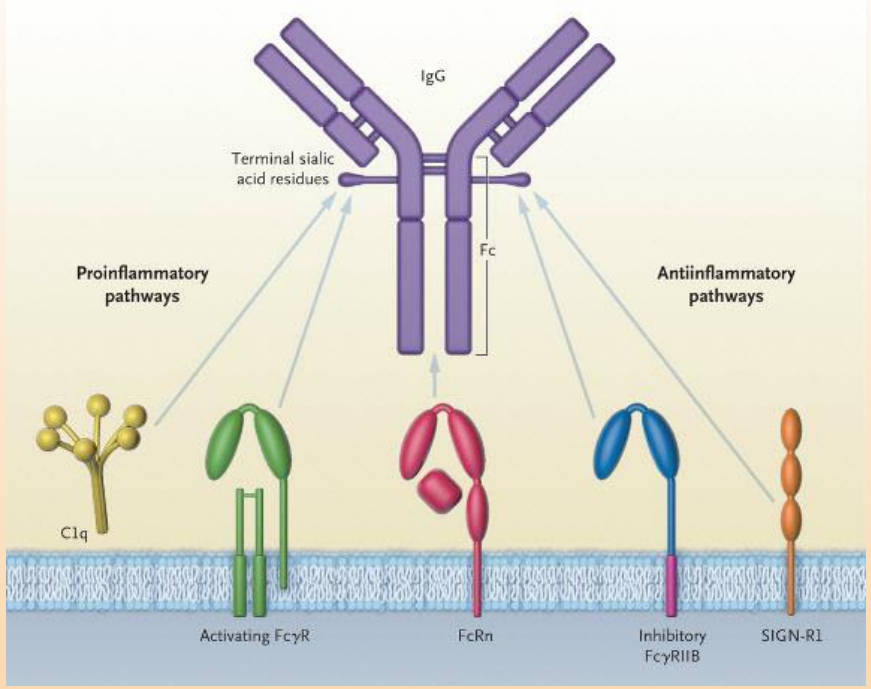
exchange with albumin

plasma volume =
0.07 x weight (kg) x (1 - hematocrit)

Treatment of ABMR IVIG

IVIG at a dose of 100 mg/kg after each session of plasmapheresis.

500 mg/kg/day 1-2 days after the final session of plasmapheresis with a total cumulative target dose of at least 1000 mg/kg of IVIG.



OPEN

Rituximab and Monitoring Strategies for Late Antibody-Mediated Rejection After Kidney Transplantation

Sandesh Parajuli, MD,[1] Didier A. Mandelbrot, MD,[1] Brenda Muth, NP,[1] Maha Mohamed, MD,[1] Neetika Garg, MD,[1] Fahad Aziz, MD,[1] Robert R. Redfield, MD,[2] Weixiong Zhong, MD, PhD,[3] Brad C. Astor, PhD,[1,4] and Arjang Djamali, MD[1,2]

sone, 100 mg bolus and taper, and IVIG, 200 mg/kg every 2 weeks × 3. Baseline immunosuppression is also increased by approximately 25%. Rituximab, 375 mg/m^2 single dose, is added based on clinical and immunophenotypic characteristics. Patients with younger age, better kidney function, higher DSA, diffuse C4d, greater microvascular inflammation, and lower chronicity score are more likely to receive rituximab. Our usual immunosuppression regimen is tacrolimus (12-hour trough goal of 5-7 ng/dL 6 months after transplant); mycophenolic acid, 720 mg twice a day; and prednisone, 5 mg daily, with doses adjusted based on adverse effects and immunological risk. Patient's baseline immunosuppressive medica-

TABLE 4.

Rituximab was associated with improved graft survival

		Changes between two biopsies and outcomes		
		Rituximab	Standard of care	*P*
Δ DSA	Mean class I MFI_{sum}	−3637 ± 5134	−2493 ± 3644	0.48
	Mean class II MFI_{sum}	−4559 ± 6938	−2378 ± 2893	0.17
	Mean MFI_{max}	−3033 ± 5179	−1501 ± 1754	0.13
Δ Kidney function	Serum creatinine (mg/dL)	0 ± 0.6	0 ± 0.8	0.94
	eGFR (mL/min/1.73 m^2)	0.7 ± 9.2	−2.8 ± 11.0	0.13
	UPC (gm/gm)	0.2 ± 1.3	0.1 ± 1.1	0.82
Δ Pathology	Microvascular injury (ptc + g)	−0.9 ± 1.5	−1.1 ± 1.3	0.46
	C4d score (range)	−0.7 ± 1.1	−0.5 ± 1.1	0.43
	Chronicity score (ci + ct + cg + cv)	0.2 ± 2.1	0.6 ± 1.8	0.42
Outcome	Serum creatinine 6 months after ABMR (mg/dL)	1.8 ± 0.7	1.8 ± 0.8	0.88
	Serum creatinine 12 months after ABMR (mg/dL)	2.2 ± 1.1	2.3 ± 1.2	0.76
	Serum creatinine on last follow-up (mg/dL)	1.96 ± 0.7	1.8 ± 0.7	0.35
	Mean number of subsequent biopsies	1.0 ± 1.2	1.8 ± 0.8	<0.001
	Graft loss	6	12	0.01
	Death	0	2	0.14

MFI, mean fluorescence intensity; eGFR, estimated glomerular filtration rate; ABMR, antibody mediated rejection; ptc, peritubular capillaritis; g, glomerulitis; ci, interstitial fibrosis; ct, tubular atrophy; cv, fibrous intimal thickening; cg, allograft glomerulopathy.

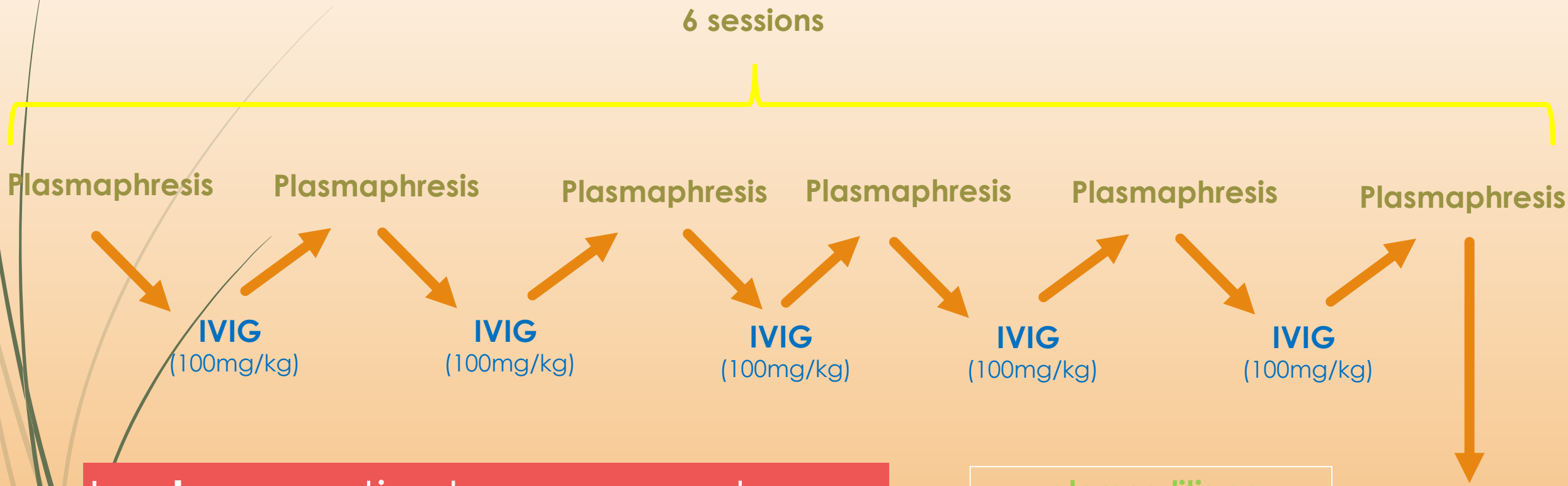
Treatment of ABMR
Rituximab

In patients with evidence of microvascular inflammation on biopsy

(glomerulitis or peritubular capillaritis)

as a single dose of 200 to 375 mg/m2

after completion of plasmapheresis and IVIG.

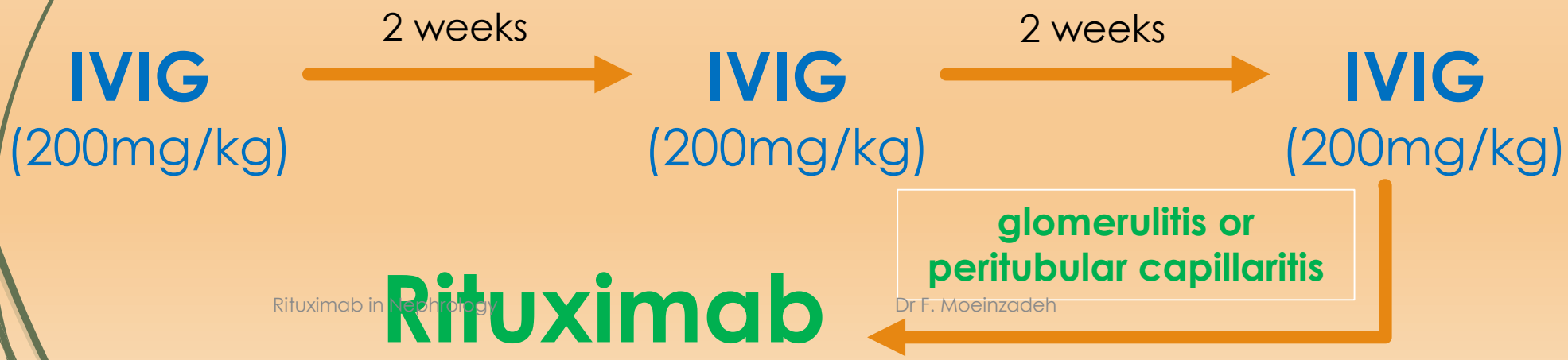


In **obese** patients, some centers determine the IVIG dose based upon the patient's **ideal body** weight.

Rituximab

ABMR after the first year

- **<u>Plasmapheresis is not performed</u>** because of the lack of evidence supporting the safety and efficacy of plasmapheresis in late-onset ABMR.
- IVIG At a dose of 200 mg/kg every two weeks for three doses.



We treat all patients with evidence of chronic ABMR using a combination of glucocorticoids and intravenous (IV) immune globulin (IVIG). We add rituximab to the treatment regimen if there is evidence of active microvascular inflammation on renal biopsy. We do **not** use eculizumab or bortezomib in the treatment of chronic ABMR. Our approach in patients with chronic ABMR is similar to that used in patients with active ABMR that occurs after the first year posttransplant. (See

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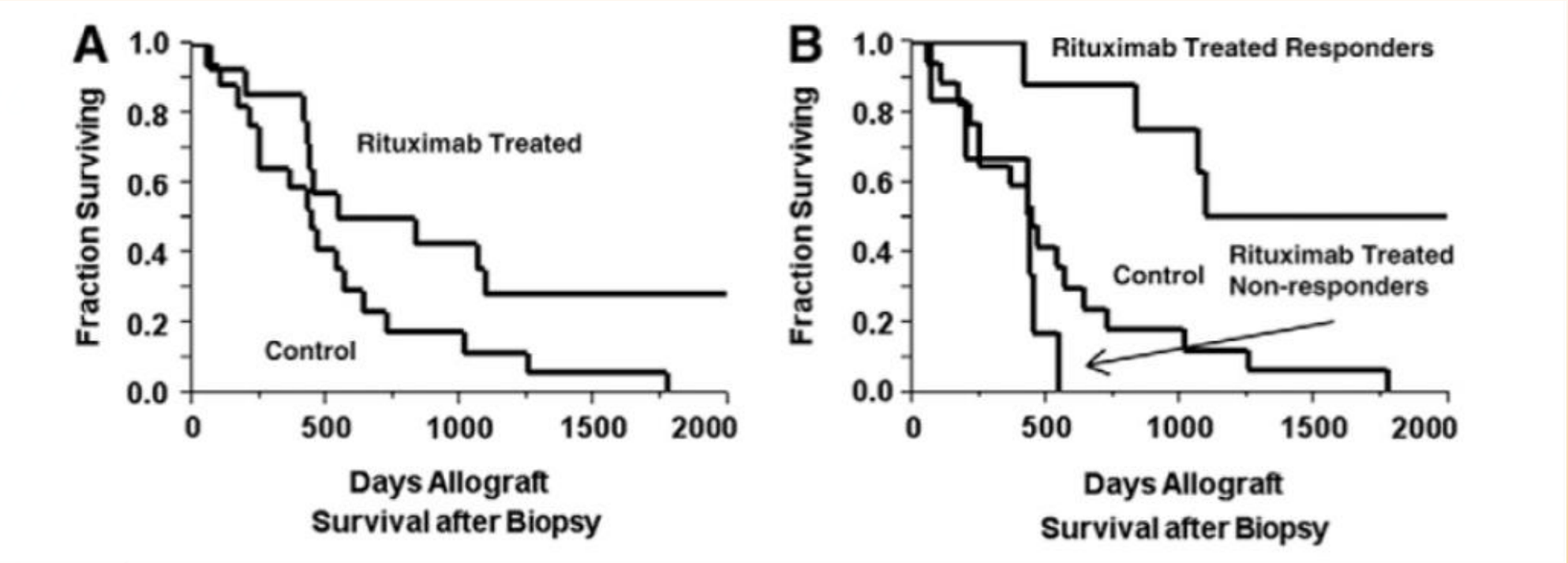
Published in final edited form as:
Transpl Immunol. 2012 October ; 27(0): 107–113. doi:10.1016/j.trim.2012.08.005.

Partial therapeutic response to Rituximab for the treatment of chronic alloantibody mediated rejection of kidney allografts⋆

R. Neal Smith[a,*], **Fahim Malik**[b], **Nelson Goes**[c], **Alton B. Farris**[d], **Emmanuel Zorn**[e], **Susan Saidman**[a], **Nina Tolkoff-Rubin**[b], **Sonika Puri**[b], and **Waichi Wong**[b]

[a]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

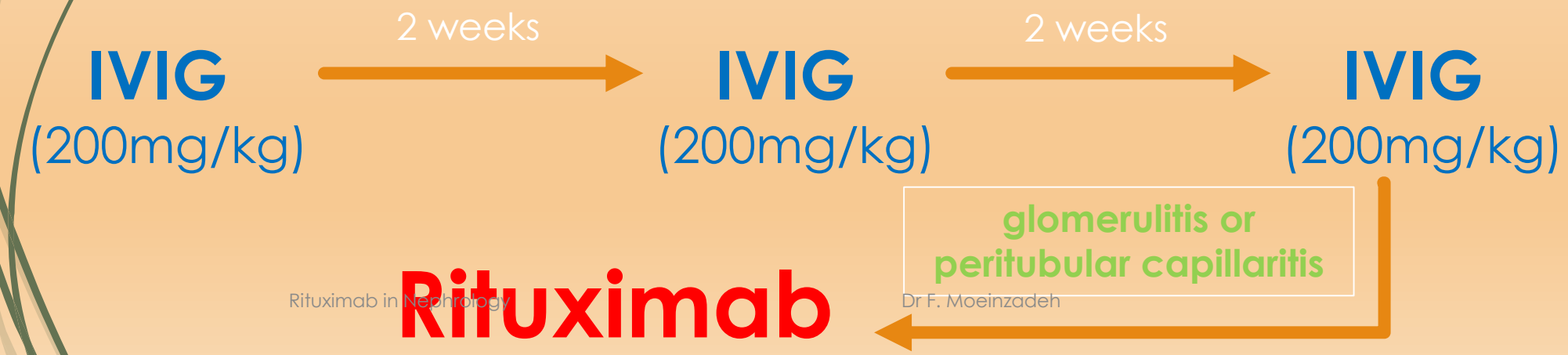
Smith RN, Malik F, Goes N, et al. Partial therapeutic response to Rituximab for the treatment of chronic alloantibody mediated rejection of kidney allografts. Transpl Immunol 2012; 27:107.



The median graft survival time was greater among patients treated with rituximab compared with those treated without rituximab (685 versus 439 days).

Smith RN, Malik F, Goes N, et al. Partial therapeutic response to Rituximab for the treatment of chronic alloantibody mediated rejection of kidney allografts. Transpl Immunol 2012; 27:107.

Tx of Chronic ABMR = after the first year



Curr Transpl Rep (2014) 1:78–85
DOI 10.1007/s40472-014-0012-y

KIDNEY TRANSPLANTATION (ML HENRY, SECTION EDITOR)

Acute Antibody-Mediated Rejection in Renal Transplantation: Current Clinical Management

Carrie Schinstock · Mark D. Stegall

Curr Transpl Rep (2014) 1:78–85

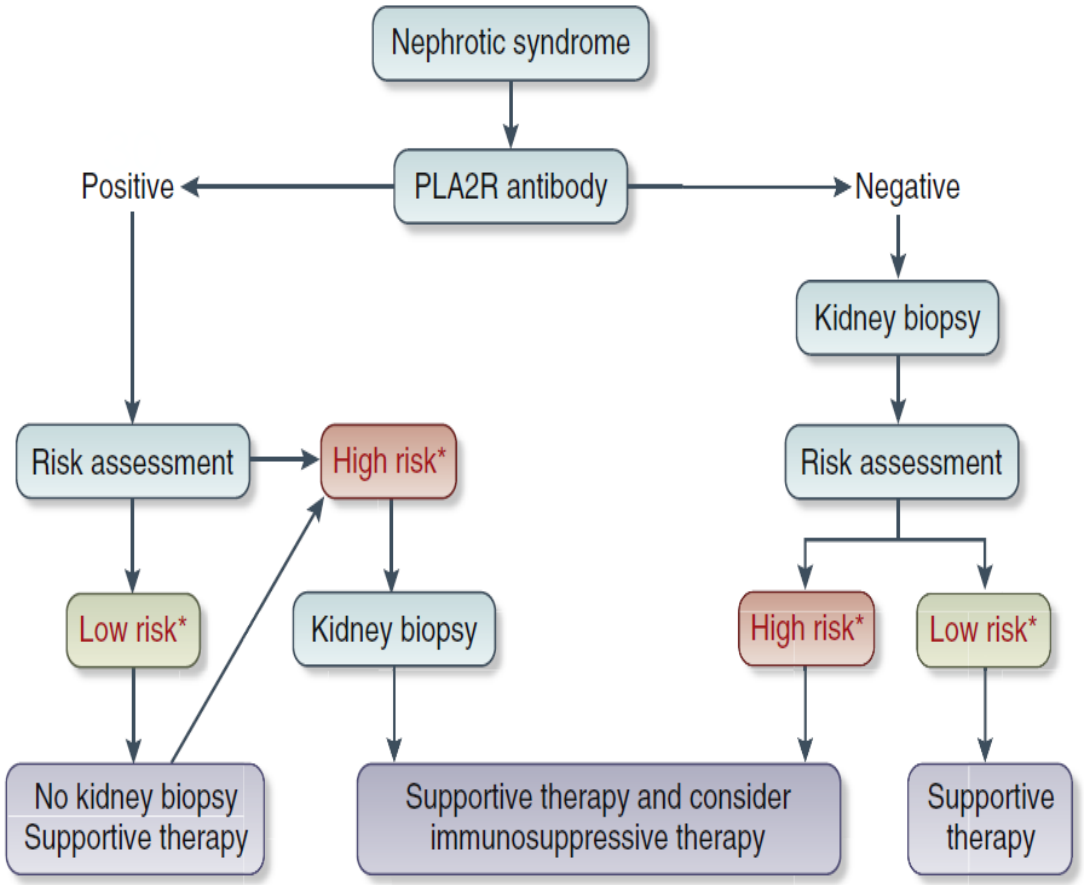
Early versus late acute AMR

	Early AMR	Late AMR
Timing	Days to weeks post-transplant	Months to years post-transplant
Pathophysiology	Levels of preformed DSA increase from memory B-cell response following antigen stimulation	Formation of de novo DSA or increase in preformed DSA in setting of suboptimal immunosuppression and/or concomitant cellular rejection
Histology	C4d+ peritubular capillaries on immunofluorescence, acute tubular necrosis, peritubular capillaritis, and glomerulitis	Similar to early AMR in most cases: Peritubular capillaritis and glomerulitis +/− C4d positivity in setting of interstitial inflammation and tubulitis. Features of transplant glomerulopathy may also be present.
Treatment	Plasmapheresis IVIG Eculizumab Bortezomib Rituximab	Treatment of cellular rejection (e.g., steroids and anti-lymphocyte therapy). Consider plasmapheresis and IVIG if DSA MFI>6000. In absence of transplant glomerulopathy, eculizumab, bortezomib, or rituximab could be considered.

Rituximab in glomerular diseases

- Membranous nephropathy
- Minimal change disease
- FSGS
- SLE

Membranous glomerulonephritis



Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Kidney International (2019) **95,** 268–280; https://doi.org/10.1016/j.kint.2018.10.018

Table 2 | Factors associated with the risk of progressive loss of kidney function in patients with membranous nephropathy

Low risk	High risk
Proteinuria <3.5 g/d	• Serum creatinine >1.5 mg/dl (133 µmol/l) • Decrease in eGFR by ≥ 20% over any time period during the preceding 12 months not explained otherwise[a] • Proteinuria >8 g/d for > 6 mo • Presence of low-molecular-weight proteinuria • Urine IgG > 250 mg/24 h • PLA2R antibody levels and evolution[b]

Membranous glomerulonephritis

- In the Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) study, rituximab was more effective than placebo in inducing remissions after 17 months
- The nonresponse rate to rituximab was approximately 35%

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Volume 9, Issue 6
December 2016

Treatment with rituximab in idiopathic membranous nephropathy

Marco Fiorentino, Francesco Tondolo, Francesca Bruno, Barbara Infante, Giuseppe Grandaliano, Loreto Gesualdo, Carlo Manno

Clinical Kidney Journal, Volume 9, Issue 6, 1 December 2016, Pages 788–793, https://doi.org/10.1093/ckj/sfw091
Published: 13 October 2016 **Article history**

- ***B cell depletion with rituximab therapy induces remission or stabilization of disease and renal function in MN patients with a high risk of progression of renal damage.***
- ***The limited adverse events described in our study suggest its efficacy and safety.***
- ***In the future, the results of randomized clinical trials should confirm these results and better define the role of rituximab treatment in MN.***

Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up

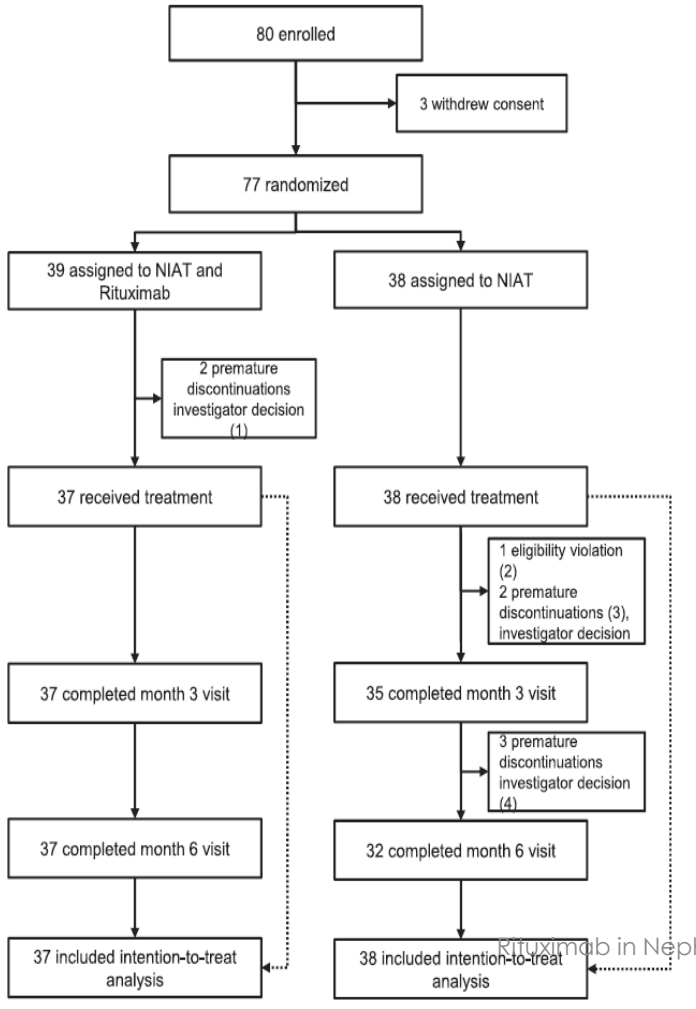


Table 3. Results of efficacy analysis at last follow-up

End Point	NIAT-Rituximab Group, *n*=37	NIAT Group, *n*=38	*P* Value
Remission, complete and partial[a]	24 (64.9; 49.5 to 80.2)	13 (34.2; 19.1 to 49.3)	<0.01
Protein-to-creatinine ratio, mg/g	2194.8 (1309.8–5310.0)	4701.1 (2027.8–8265.3)	0.02
Serum albumin, g/L	32 (26–35)	27 (20–30)	0.03
Serum creatinine, μmol/L	101 (87–135)	97.2 (78.5–133.5)	0.50
eGFR, ml/min per 1.73 m^2	61.1 (48.7–83.4)	73.1 (50.4–90.5)	0.48

CLINICAL RESEARCH www.jasn.org

Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up

- In conclusion, this trial shows that serum albumin and PLA2R-Ab levels are early markers of NIAT-rituximab efficacy, whereas the effect on proteinuria remission appears after 6 months.
- Addition of rituximab to NIAT has no effect on safety.
- This first RCT is another step toward the use of rituximab as first-line therapy in severe forms of PMN.
- It also suggests that criteria for definition of remission should include serum albumin and PLA2R-Ab levels, particularly in trials where rapid responses on drug efficacy and surrogate criteria are needed.

CLINICAL EPIDEMIOLOGY www.jasn.org

Safety of Rituximab Compared with Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy

- Although the cumulative incidence of partial remission was lower in the RTX group, rates of complete remission and the composite renal end point did not differ significantly between groups.
- Because of its superior safety profile, we suggest that RTX might replace ST-CP as first line immunosuppressive therapy in patients with idiopathic membranous nephropathy and nephrotic syndrome.

J Am Soc Nephrol 28: 2729–2737, 2017

Safety of Rituximab Compared with Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy

Table 3. Nonserious events and patients with event throughout the whole observation period according to treatment group

Type of event	RTX, *n*=100	ST-CP, *n*=103
Myelotoxicity		
Pancytopenia	0	1
Leukopenia and anemia	0	5
Anemia	0	11[a]
Leukopenia	0	35[b]
Thrombocytopenia	0	7[c]
Total	0	59[b]
Minor cardiovascular disease	3	0
Infections		
Respiratory tract	4	15[b]
Urinary tract	0	1
Herpes zoster	0	7[c]
Other/unspecified	3	14[a]
Total	7	37[b]
Infusion reactions[d]	28	0[b]
Other events	8	11
Liver toxicity	1	7
Hyperglycemia	2	10[c]
Total	3	28[b]
Total no. of nonserious events	52	127
Patients with nonserious events[e]	41	58

Focal Segmental Glomerulosclerosis

- One of the most common patterns of glomerular injury
- It is the most common cause of proteinuria in the African-American &Hispanic populations
- Primary & Secondary type

KDIGO Clinical Practice Guideline for Glomerulonephritis 2012

Treatment Options

- **Corticosteroid and immunosuppressive only in idiopathic FSGS & features of the nephrotic syndrome (1C)**
  - **1mg/kg (max80mg) or alternate-day 2 mg/kg(max120mg) (2C) Initial high dose for at least of 4 weeks**
  - **High-dose corticosteroids ,max of 16 weeks, as tolerated, or until complete remission (2D)**
  - **Tapered slowly over a period of 6 months after achieving CR (2D)**
- **CNIs as first-line therapy for relative contraindications or intolerance to high-dose corticosteroids (2D)**
- **Steroid-resistant , who do not tolerate cyclosporine:**
  - **Combination of MMF and high-dose dexamethasone. (2C)**

KDIGO Clinical Practice Guideline for Glomerulonephritis 2012

American Journal of Nephrology

Original Report: Patient-Oriented, Translational Research

Am J Nephrol 2017;46:108–113
DOI: 10.1159/000477944

Received: March 10, 2017
Accepted: May 30, 2017
Published online: July 13, 2017

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

- Eight patients biopsy-proven FSGS (4 women, 4 men)
- High dose (8 weekly -375 mg/m2) follow for at least 2 years
- Failed to improve proteinuria in 7 out of 8 patients, with persistent nephrotic proteinuria.
- In one , a rapidly deteriorating renal function was also observed

Focal Segmental Glomerulosclerosis & Minimal change disease

- Data are emerging to support an early role of RTX in the management of children with steroid-dependent nephrotic syndrome.
- RTX is an emerging second-line therapy in MCD in adults although evidence is observational only.
- The recommendation for CNIs and MMF as second- and third-line treatments, respectively, for FSGS should be maintained.
- Randomized controlled trials are underway to investigate the value of RTX in adult MCD
- Several case reports : Successful use of in adult patients with steroid-dependent but not steroid-resistant

➢ In steroid-resistant FSGS did not induce remission

Rituximab for Recurrence of Primary Focal Segmental Glomerulosclerosis After Kidney Transplantation: Clinical Outcomes.

Garrouste C[1], Canaud G, Büchler M, Rivalan J, Colosio C, Martinez F, Aniort J, Dudreuilh C, Pereira B, Caillard S, Philipponnet C, Anglicheau D, Heng AE.

Author information

Abstract

BACKGROUND: Rituximab has shown encouraging results for the treatment of kidney transplantation recipients with focal segmental glomerulosclerosis (FSGS) recurrence. However, the correct, opportune, and safe use of rituximab for this indication remains to be determined.

METHODS: This multicenter retrospective study reports on 19 new cases aged 35 (15-66) years who developed FSGS recurrence at 12 (1.5-27) days posttransplantation. Initial treatment consisted of plasma exchanges (PE), high doses of calcineurin inhibitors, and steroids. Rituximab was introduced either immediately (N = 6) or after failure of the initial treatment (N = 10) or failed attempted weaning from PE (N = 3).

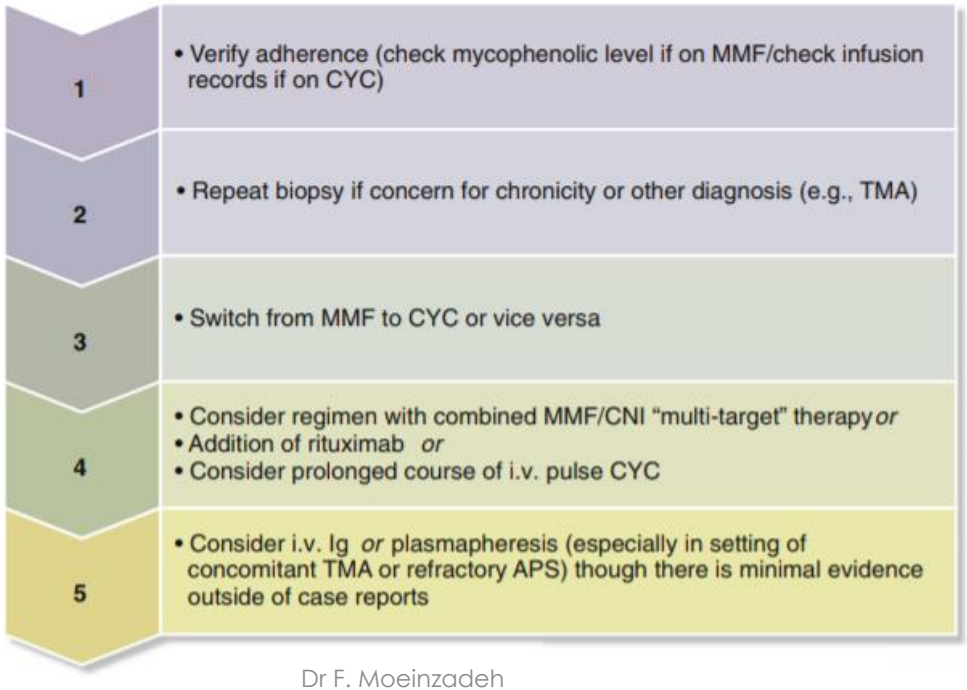
RESULTS: Overall, we observed 9 of 19 complete remissions and 3 of 19 partial remissions. Estimated glomerular filtration rates (Modification of Diet in Renal Disease 4) were significantly higher in the responding patients than in nonresponding patients at month (M)12, M36, and M60. Overall, kidney survival at 5 years was 77.4% (95% range, 41.9-92.7). The 5-year graft survival rates in the responding patients and the nonresponding patients were 100% and 36.5%, respectively (P = 0.01). A further course of rituximab was required for 4 patients as a result of FSGS relapse, with good results. During the first year after renal transplantation, 14 patients developed severe infections (16 bacterial, 4 viral, 1 parasitic).

CONCLUSIONS: In kidney transplantation recipients with recurrent FSGS, rituximab therapy may be a recommended treatment for cases that have failed either the initial treatment or weaning from PE.

PMID: 27043407 DOI: 10.1097/TP.0000000000001160

Systemic lupus erythematosis

- Preliminary studies suggest that intensive B-cell depletion with a RTX plus CYC-based regimen may avoid the need for maintenance therapy



Kidney International (2019) **95,** 281–295

Figure 1 | Algorithm for refractory disease in lupus nephritis. APS, antiphospholipid syndrome; CNI, calcineurin inhibitor; CYC, cyclophosphamide; MMF, mycophenolate mofetil; TMA, thrombotic microangiopathy.

ANCA-ASSOCIATED VASCULITIS

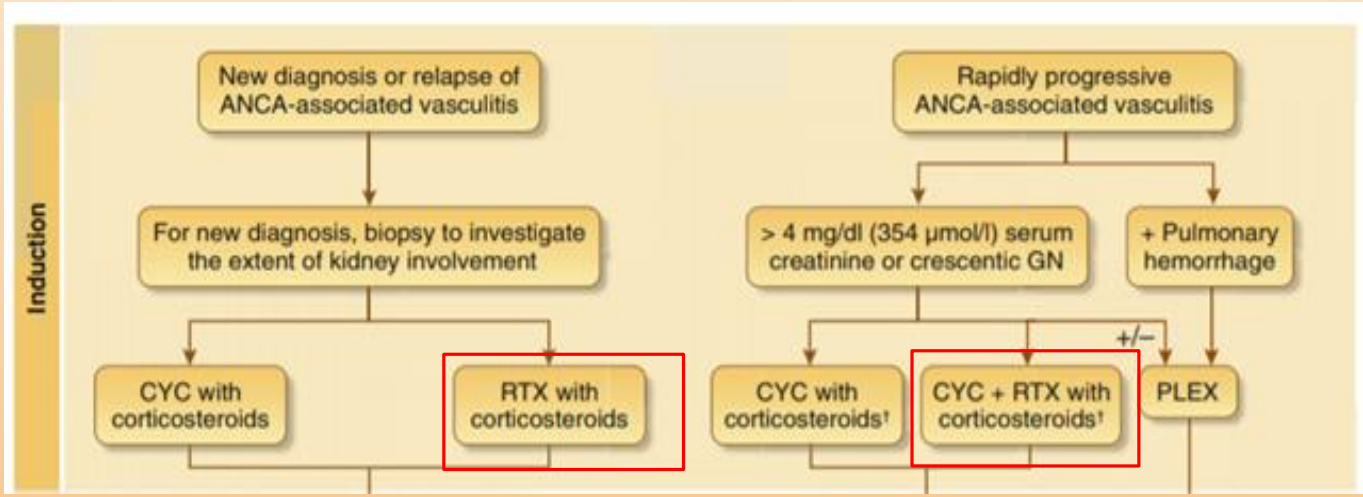


Figure 2| Treatment algorithm for anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis. Remission is defined by the absence of manifestations of vasculitis and glomerulonephritis disease activity (Birmingham Vasculitis Activity Score for Wegner granulomatosis [BVAS/WG] of 0). For glomerulonephritis (GN), remission is considered as absence of microscopic hematuria and improved proteinuria and glomerular filtration rate. *Based on peripheral B-cell repopulation plus ANCA reappearance. †In patients with rapidly deteriorating kidney function, corticosteriods are often initiated i.v. as pulse doses of 500 to 1000 mg/d methylprednisone and given for 1 to 3 days before converting to an oral formulation. ‡Consider re-biopsy in order to guide second-line therapy. AZA, azathioprine; CYC, cyclophosphamide; PLEX, plasma exchange; PR3, proteinase 3; RTX, rituximab.

ANCA-ASSOCIATED VASCULITIS

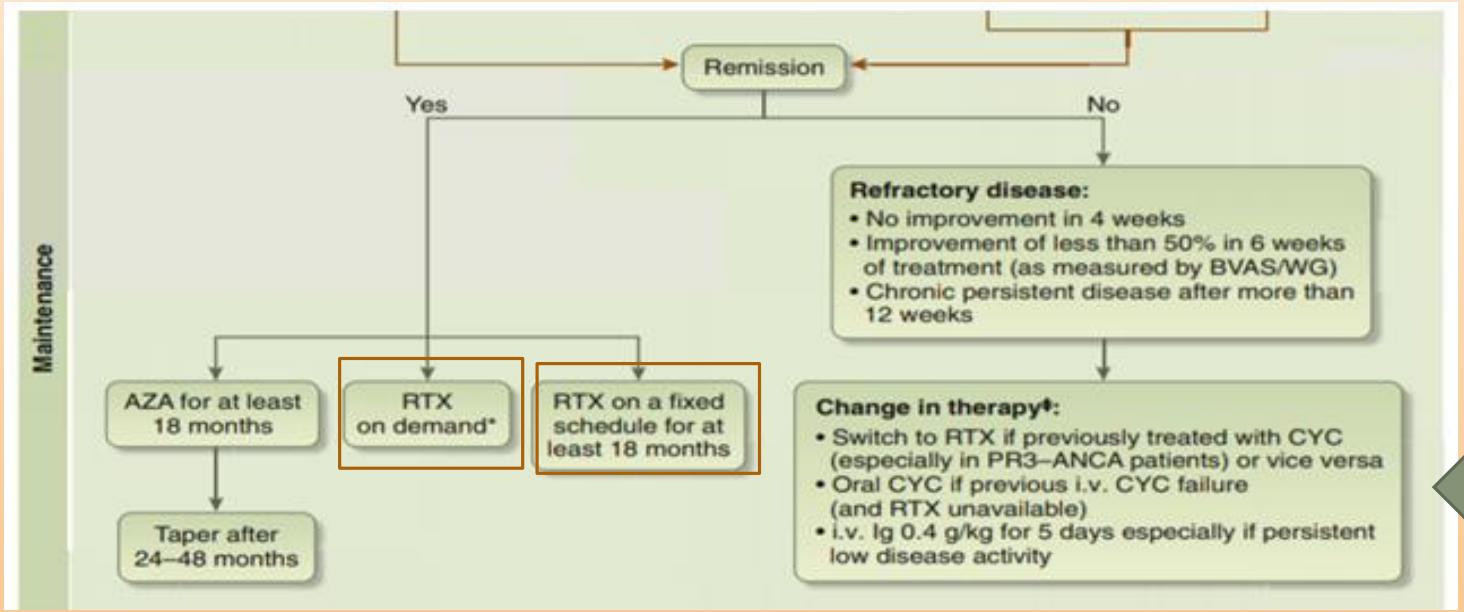


Figure 2| Treatment algorithm for anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis. Remission is defined by the absence of manifestations of vasculitis and glomerulonephritis disease activity (Birmingham Vasculitis Activity Score for Wegner granulomatosis [BVAS/WG] of 0). For glomerulonephritis (GN), remission is considered as absence of microscopic hematuria and improved proteinuria and glomerular filtration rate. *Based on peripheral B-cell repopulation plus ANCA reappearance. †In patients with rapidly deteriorating kidney function, corticosteriods are often initiated i.v. as pulse doses of 500 to 1000 mg/d methylprednisone and given for 1 to 3 days before converting to an oral formulation. ‡Consider re-biopsy in order to guide second line therapy. AZA, azathioprine; CYC, cyclophosphamide; PLEX, plasma exchange; PR3, proteinase 3; RTX, rituximab.

ANCA-ASSOCIATED VASCULITIS

Table 5 | Examples of various rituximab-based regimens for induction and remission in AAV that have been used in the literature

Induction
Four weekly i.v. doses of 375 mg/m^2,[171,172] or 2 biweekly doses of 750 mg/m^2 (maximum dose 1000 mg)[182]
Four weekly i.v. doses of 375 mg/m^2 and 1 monthly infusion 1 and 2 months apart[179,186]
Maintenance
750 mg/m^2 (maximum dose 1000 mg) every 6 months[180–183]
750 mg/m^2 (maximum dose 1000 mg) every 4 months[181]
750 mg/m^2 (maximum dose 1000 mg) every 6 months for 24 months[184]
750 mg/m^2 (maximum dose 1000 mg) every 12 months[183]
375 mg/m^2 every 6 months[183]
500 mg on days 1 and 15, then 5.5 months later, and again every 6 months for a total of 5 doses over 18 months[185]

AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis.

conclusion

- In acute & chronic ABMR: after plasmaphresis and IVIG
- In membranous GN: primary use or in high risk group
- In FSGS: primary: unknown
- Post transplantation: used
- In SLE: in refractory SLE
- In ANCA associated vasculitis: approved

Thanks for attention