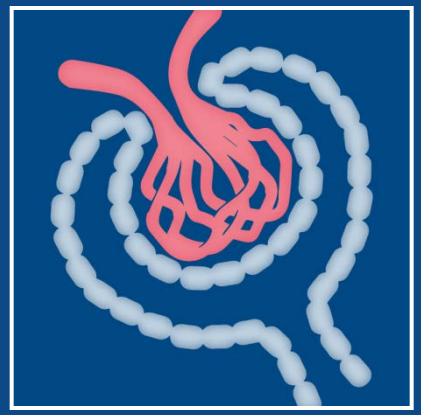
Nephro Update Europe 2017

6-7 October, Vienna

Glomerulonephritis



Jack Wetzels, The Netherlands

Primary Glomerulonephritis: Membranous Nephropathy

Membranous Nephropathy: State of the Art

- Most common cause of nephrotic syndrome in adults
- 2009: anti-PLA2R antibodies

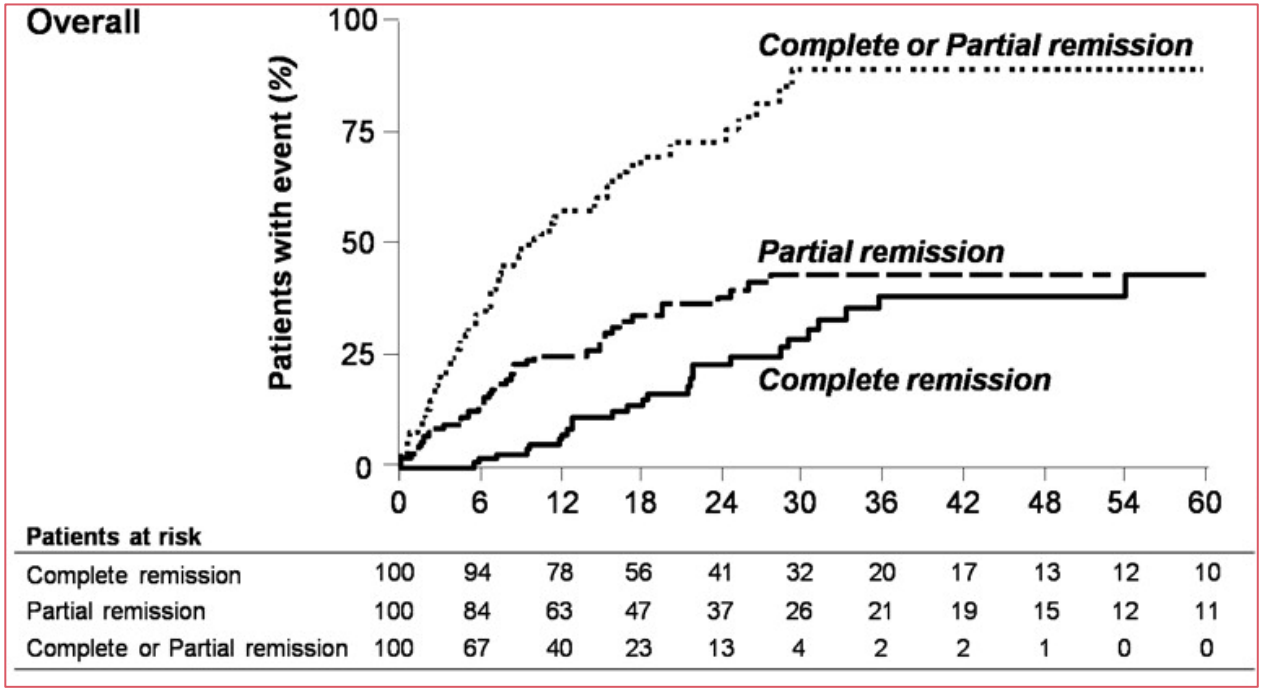
KDIGO guidelines:

- Immunosuppressive therapy in *high risk* patients *(proteinuria > 4g/day and >50% over baseline after 6 months conservative therapy [OR] ΔScreat > + 30%)*
- 1st Cyclophosphamide and prednisone
- 2nd Calcineurin inhibitors *(not proven effective on hard renal end-points; awaiting RCT's MENTOR and STARMEN)*
- No specific recommendations regarding Rituximab *(in view of the lack of RCT's)*

Kidney disease: Improving Global Outcome (KDIGO) Glomerulonephritis Work Group: KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int, Suppl 2012; 2: 186-197

Membranous Nephropathy: State of the Art

- In 2012 Rituximab was proposed as 1st line therapy for patients with primary MN

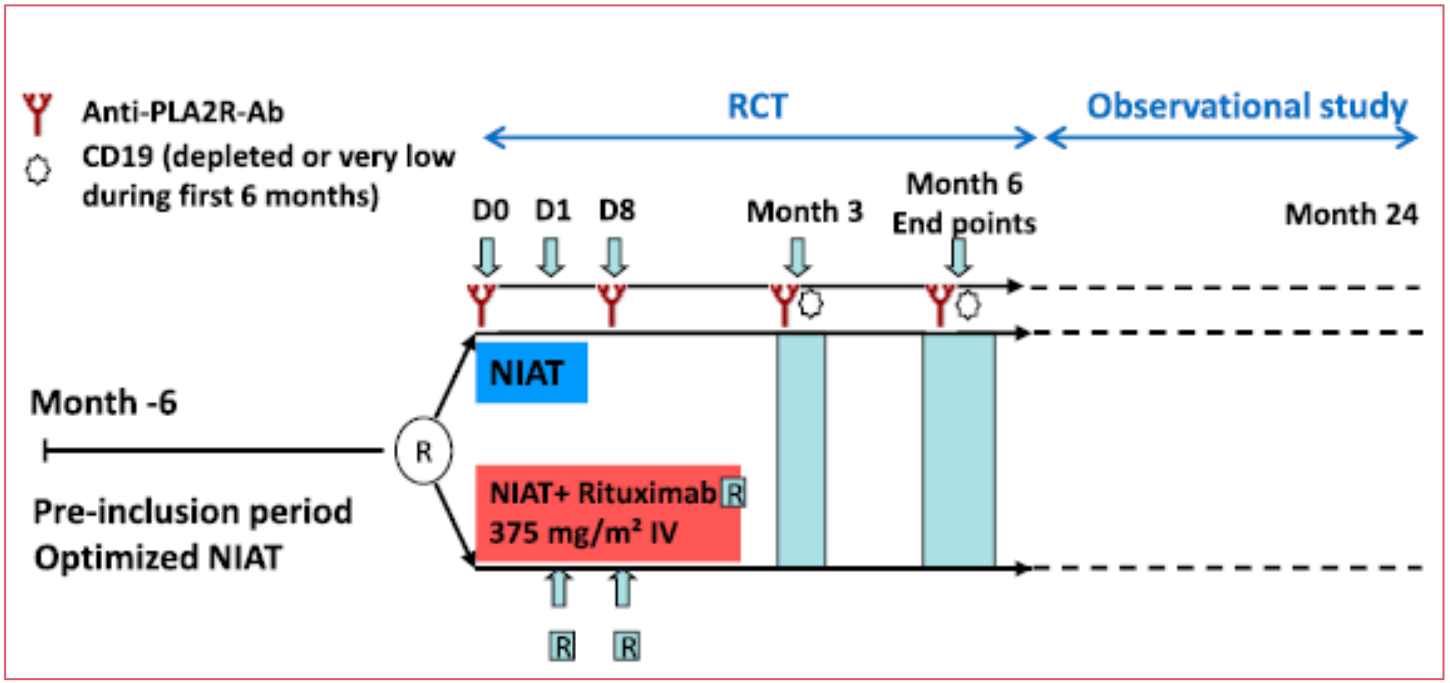


Patients at risk											
Complete remission	100	94	78	56	41	32	20	17	13	12	10
Partial remission	100	84	63	47	37	26	21	19	15	12	11
Complete or Partial remission	100	67	40	23	13	4	2	2	1	0	0

Ruggenenti P et al. J Am Soc Nephrol 2012; 23: 1416-1423

Membranous Nephropathy: Rituximab RCT

- GEMRITUX: Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy Study
- Rituximab 2 * 375 mg/m2 vs control



Dahan K et al. J Am Soc Nephrol 2017; 28: 348 - 358

Membranous Nephropathy: Rituximab RCT

- GEMRITUX: Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy Study
- Patient characteristics

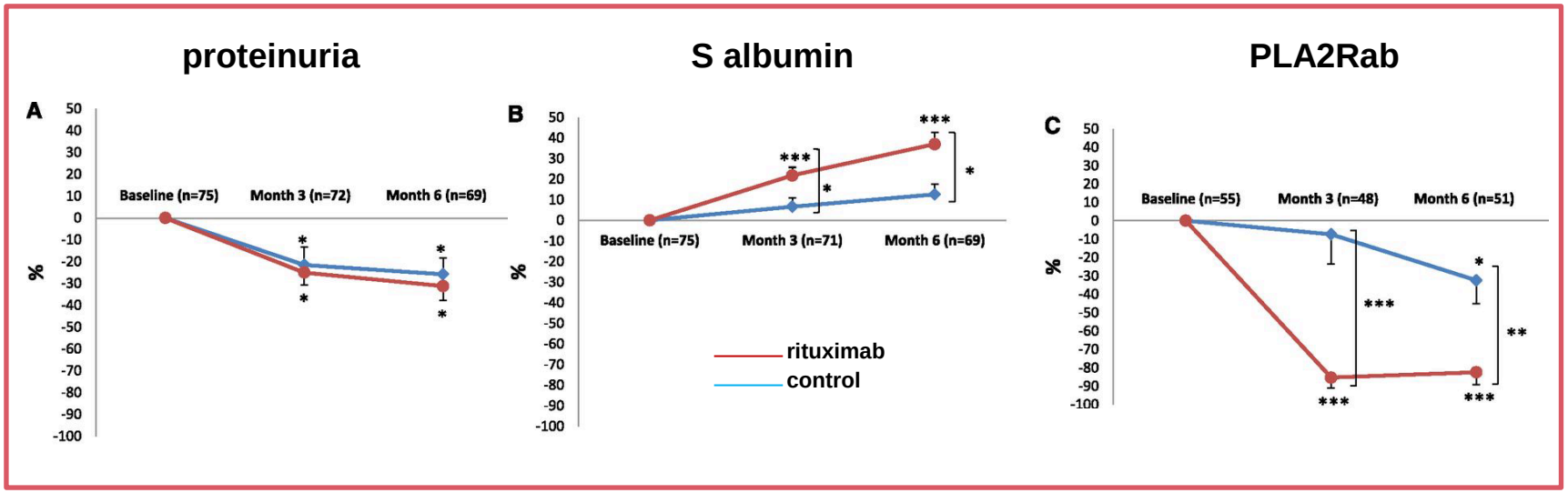
	Control (n = 38)	Rituximab (n = 37)
Gender (% Male)	24 (63%)	28 (76%)
Age (yrs)	59 (43-64)	53 (42-63)
S creat (umol/l)	91 (74-122)	98 (73-123)
S albumin (g/l)	22 (20-26)	22 (18-25)
Proteinuria (g/day)	7.2 (5.4-9.0)	7.7 (4.6-10.4)
Disease Duration (mo)	8 (6-11)	8 (6-13)
PLA2Rab positive	28 (74%)	27 (73%)

Dahan K et al. J Am Soc Nephrol 2017; 28: 348 - 358

Membranous Nephropathy: Rituximab RCT

- GEMRITUX: Outcome

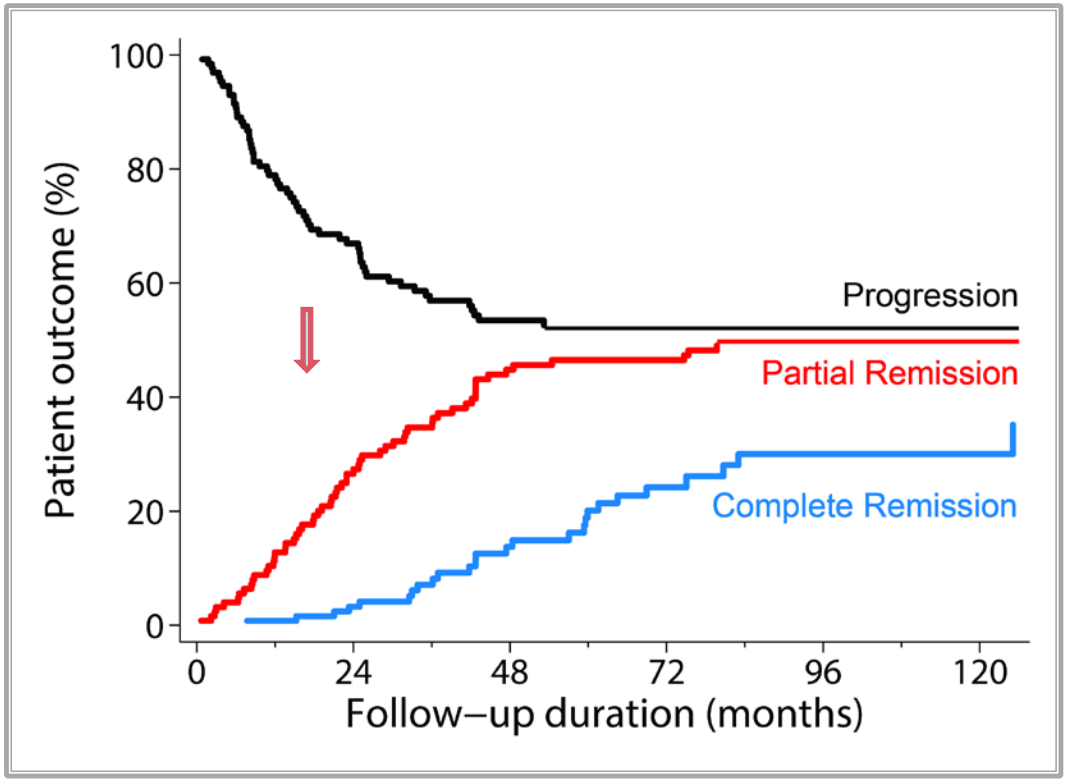
	Control (n = 38)	Rituximab (n = 37)	P-value
Remission (6 months)	8 (21%)	13 (35%)	0.21
Remission FU (17 months)	13 (34%)	24 (65%)	< 0.01



Dahan K et al. J Am Soc Nephrol 2017; 28: 348 - 358

Membranous Nephropathy: lessons from GEMRITUX

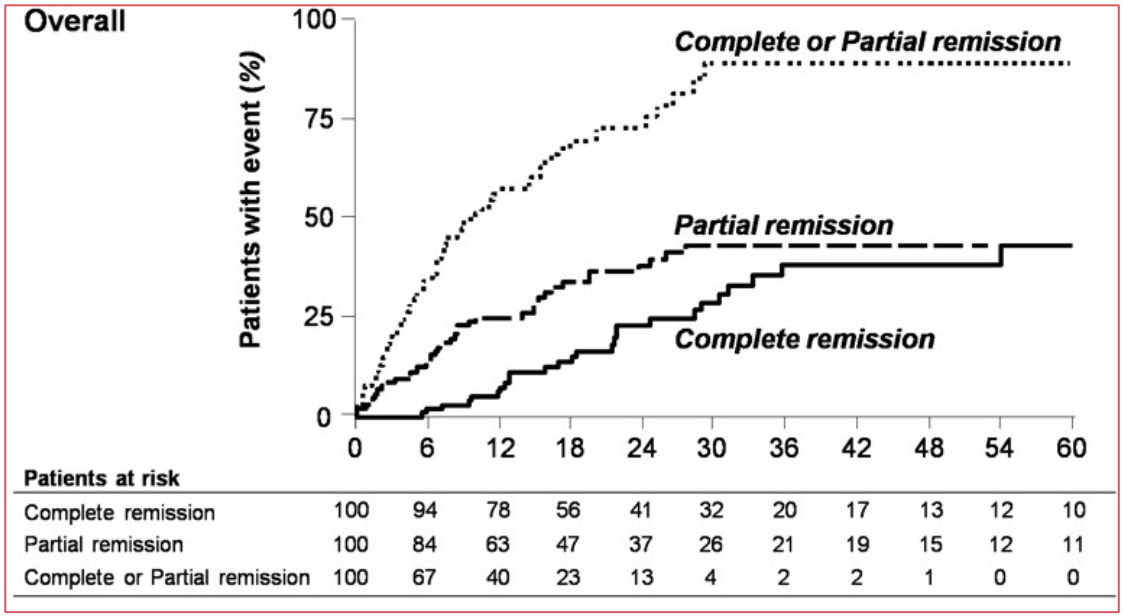
- Risk prediction not accurate
- 34% remission after 17 months → more after 3 yrs?



Van de Brand J et al. Clin J Am Soc Nephrol 2012; 7: 1242-1248

Membranous Nephropathy: lessons from GEMRITUX

- Rituximab: many non-responders (already known)



n =100

No response 35%

Relapse 27% after 29 mo

Ruggenenti P et al. J Am Soc Nephrol 2012; 23: 1416-1423

Membranous Nephropathy: lessons from GEMRITUX

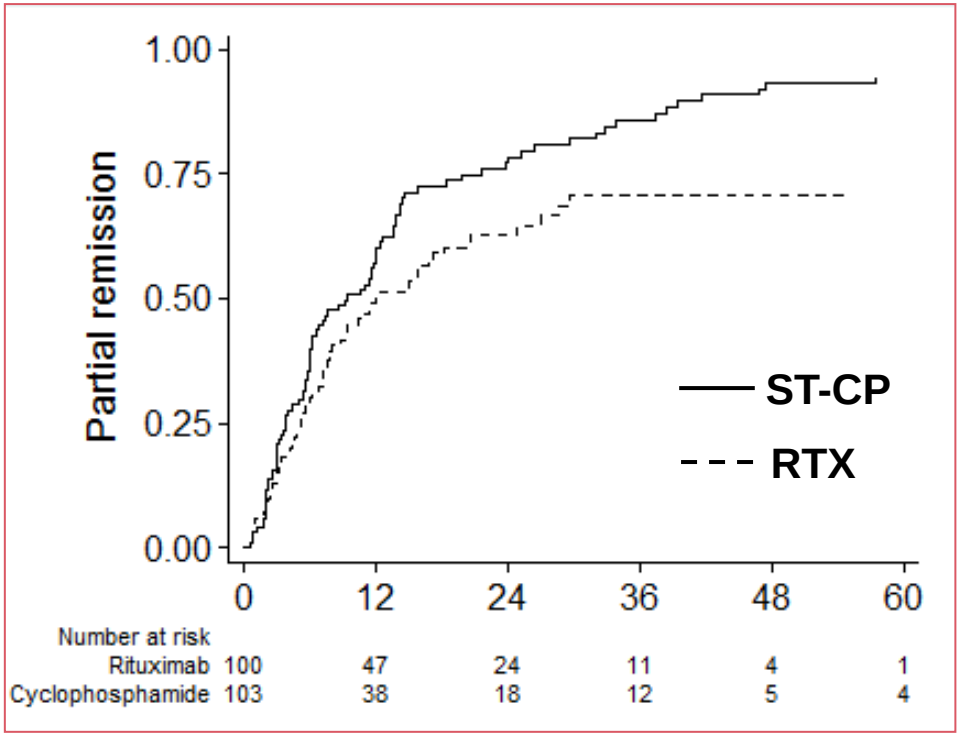
- Rituximab less effective than cyclophosphamide?

Rituximab:

Fewer (S)AE's

Complete remissions ~
Renal failure ~

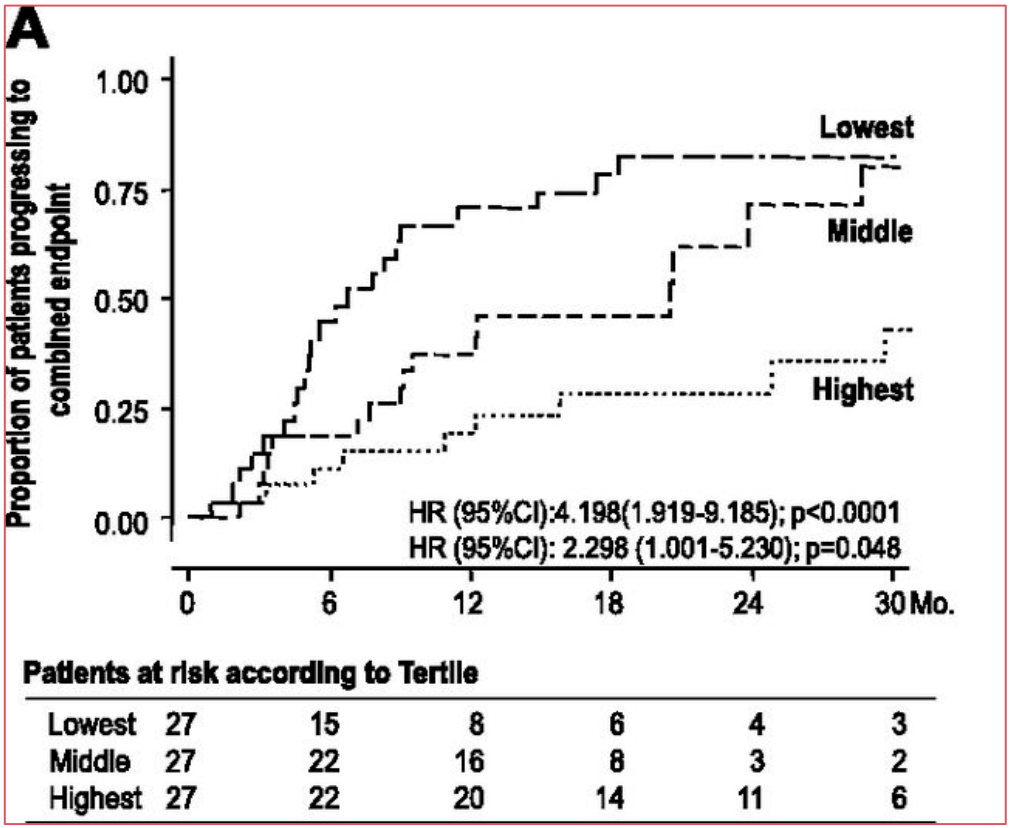
Partial remissions: ↓



Van den Brand J et al. J Am Soc Nephrol 2017; **May 9. pii: ASN.2016091022. doi: 10.1681/ASN.2016091022**

Membranous Nephropathy: lessons from GEMRITUX

- Rituximab less effective in patients with high aPLA2Rab



Ruggenenti P et al. J Am Soc Nephrol 2015; 26: 2545-2558

Membranous Nephropathy: Take Home Message

- KDIGO criteria for defining high risk are insufficient
- Rituximab: effective, but high non-response rate
- Anti-PLA2Rab titer might allow better prediction of risk ***AND*** treatment response
- Cyclophosphamide still valuable, especially in patients at highest risk
- Results of MENTOR (2017) and STARMEN (2018) expected.

Primary Glomerulonephritis: IgA Nephropathy

IgA Nephropathy: State of the Art

- Most common primary glomerulonephritis in the world
- Variable clinical course: isolated hematuria -- RPGN

KDIGO guidelines:

- Optimized conservative therapy with ACEi or ARB
  (RR < 125/75 mm Hg, proteinuria < 0.5 – 1.0 g/day)
- **"we suggest"** 6 months prednisone in patients with proteinuria > 1 g/day and eGFR > 50 ml/min

STOP-IgAN: questioned the efficacy of immunosuppressive therapy

Kidney disease: Improving Global Outcome (KDIGO) Glomerulonephritis Work Group: KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Inter, Suppl 2012; 2: 209-217
Rauen et al New Engl J Med: 2015; 373: 2225 - 2236

IgA Nephropathy: new RCT‘s

- Supportive versus Immunosuppressive therapy for the treatment of progressive IgA nephropathy (STOP-IgAN)
  - Prednisone (+/- Cyclophosphamide) vs control
- Therapeutic Evaluation of Steroids in IgA Nephropathy Global Testing (TESTING)
  - Prednisolone vs placebo
- The Effect of Nefecon® in Patients With Primary IgA Nephropathy at Risk of Developing End-stage Renal Disease (NEFIGAN)
  - Targeted-release Budesonide vs placebo

Rauen T et al. New Engl J Med: 2015; 373: 2225-2236; Lv J et al. JAMA 2017; 318: 412-422; Fellström B et al Lancet 2017; 389: 2117-2227

IgA Nephropathy: new RCT‘s

	STOP-IgAN	TESTING	NEFIGAN
Patients (N)	80 (C) + 82 (T)	126 (C) + 136 (T)	50 (C) + 99 (T_{1+2})
Age (years)	44	38	39
Gender (% male)	78	63	71
eGFR (ml/min/1.73m^2)	59	59	78
Proteinuria (g/d)	1.7	2.4	1.2
RR (mmHg)	125/77	124/79	128/80
Hematuria (%)	79	62	77
Follow-up (years)	3	2.1	0.75
remarks	Run in: 6 months; proteinuria 0.75- 3.5 g/day, eGFR > 30 ml/min; treatment with P (eGFR > 60) or P+CP (eGFR 30-60)	Run in : 3 months; eGFR 20- 120 ml/min; proteinuria > 1 g/day; treatment with oral prednisolone 0.6-0.8 mg/kg/day * 2 months + taper; Trial stopped prematurely SAE	Run in: 6 months; treatment with oral TRF-Budosenide 8 or 16 mg
	Germany	China + Australia	Europe

Rauen T et al. New Engl J Med: 2015; 373: 2225-2236; Lv J et al. JAMA 2017; 318: 412-422; Fellström B et al Lancet 2017; 389: 2117-2227

IgA Nephropathy: new RCT's outcome

	STOP-IgAN		TESTING		NEFIGAN	
	Control	Therapy	Control	Therapy	Control	Therapy
1^0 end point (%) full remission "renal death" Δ UPCR	5	17	16	6	+2.7%	-24.4%
Prot-Remission (%)	11	24	21	48		
ESRD (%)	8	8	8	3	-	-
Δ eGFR (ml/min/yr)	-1.6	-1.4	-6.9	-1.8	-6.0	+1.0
Hematuria-remission (%)	16	42	36	59	0	25
remarks	1^0 end-point: proteinuria < 0.2 g/d and ΔeGFR < 5 ml/min in 3 years		1^0 end-point: ESRD or ΔeGFR > 40% or death from kidney failure.		1^0 end-point: decrease geometric least-squares mean proteinuria; hematuria remission only in high dose group	
SAE	Treatment: more infections, diabetes, weight gain		Treatment: More infections, bone abn.		Treatment: Cushing, hirsutism, mood swings; Withdrawal: 2/51 C, 5/51 low dose, 11/48 high dose!	

Rauen T et al. New Engl J Med: 2015; 373: 2225-2236; Lv J et al. JAMA 2017; 318: 412-422; Fellström B et al Lancet 2017; 389: 2117-2227

IgA Nephropathy: Take Home Message

- Maximal supportive therapy is needed in IgAN. Target low BP (< 125/75 mmHg), don‘t be afraid for ACEi+ARB, consider dietary sodium, lower cholesterol

- Prednisone reduces proteinuria and hematuria in IgAN (both important predictors of outcome)
- Prednisone attenuates decrease of eGFR in progressive IgAN

→ ***Consider prednisone in progressive IgAN (ΔeGFR > 3ml/min/yr; marked proteinuria > 1.5 – 2.5 g/day)***

- Budosenide reduces proteinuria; long-term benefits ??

Primary Glomerulonephritis: Minimal Change Disease/FSGS

MCD/FSGS: State of the Art

- Most common causes of idiopathic nephrotic syndrome.
- Pathogenesis: unresolved, circulating factors?
- Two diseases or different manifestations of one disease?
- Steroid-responsiveness better predictor than histology

KDIGO guidelines:

- Initial therapy with prednisone (1mg/kg/day) until complete remission for a maximum period of 16 weeks, with taper thereafter (for children see KDIGO guideline)

- Evidence mainly based on RCT‘s in children

Kidney disease: Improving Global Outcome (KDIGO) Glomerulonephritis Work Group: KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Inter, Suppl 2012; 2: 163-185

MCD/FSGS: State of the Art

Unmet needs in MCD/FSGS

- Limit prednisone dosage (side effects)
- More than 50% of patients will relapse, some frequent (FRNS), some while using prednisone (SDNS)
- 10-40% of patients are steroid-resistent (SRNS)

KDIGO guidelines:

- SRNS: treatment with CNI or mycofenolate mofetil
- FRNS/SDNS: oral cyclophosphamide; or CNI, or mycofenolate mofetil.

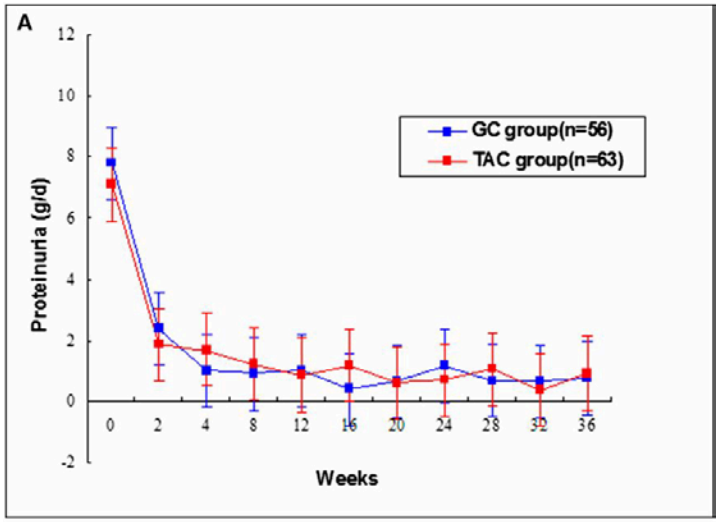
Kidney disease: Improving Global Outcome (KDIGO) Glomerulonephritis Work Group: KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Inter, Suppl 2012; 2: 163-185

MCD/FSGS: less prednisone?

- RCT: open label, non-inferiority
- Adult patients with new onset MCD
- Induction therapy: methylprednisolone (0.8 mg/kg i.v , 10 days)
- Randomisation:
  - oral prednisone 1 mg/kg/day (8 weeks + taper; total 36 weeks)
  - Tacrolimus 0.05 mg/kg/day (20 weeks target 4 – 8 ng/ml; thereafter 2 – 5 ng/ml; total duration 36 weeks)
- Outcome: remission, time to remission, relapse

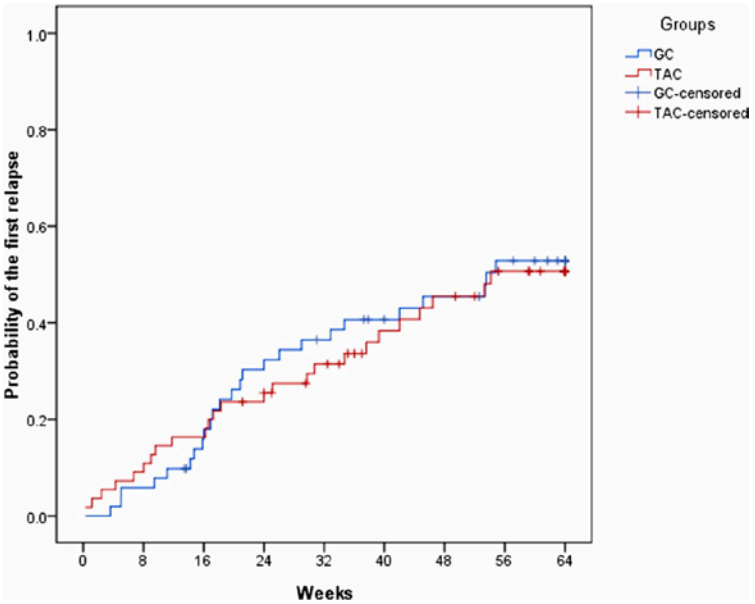
Li X et al. J Am Soc Nephrol 2017; 28: 1286-1295

MCD/FSGS: less prednisone?



Tacrolimus: non inferior with comparable remission and relapse rates

Tacrolimus: fewer side effects (Cushing, skin bruising)



Li X et al. J Am Soc Nephrol 2017; 28: 1286-1295

MCD/FSGS: prevent relapses during infections?

- RCT: double blind, placebo-controlled, cross-over with periods of one year
- Children with SDNS in remission, off steroids > 3 months
- In case of upper respiratory tract infection start prednisone 0.5 mg/kg * 5 days
- Outcome: relapse rate

Abeyagunawardena Ped Nephrol 2017; 32: 1377-1382

MCD/FSGS: prevent relapses during infections?

	GROUP 1 (prednisone-placebo)	Group 2 (Placebo-prednisone)
Patients (N)	27	21
Excluded (N)*	8	7
Gender (M/F)	12/7	9/5
Age at onset (yrs)	4.6	3.5
Age at study entry (yrs)	12.3	9.9
UTRI (N)		
First year	68	41
Second year	60	47

* non-compliance; UTRI = upper respiratory tract infection

Abeyagunawardena Ped Nephrol 2017; 32: 1377-1382

MCD/FSGS: prevent relapses during infections?

	Prednisone	Placebo
Patients (N)	33	33
UTRI (N)	115	101
Relapses	11	25*
Number of patients with		
0 relapse	22	14
1 relapse	11	13
2 relapse	0	6

UTRI = upper respiratory tract infection; * P < 0.05)

Abeyagunawardena Ped Nephrol 2017; 32: 1377-1382

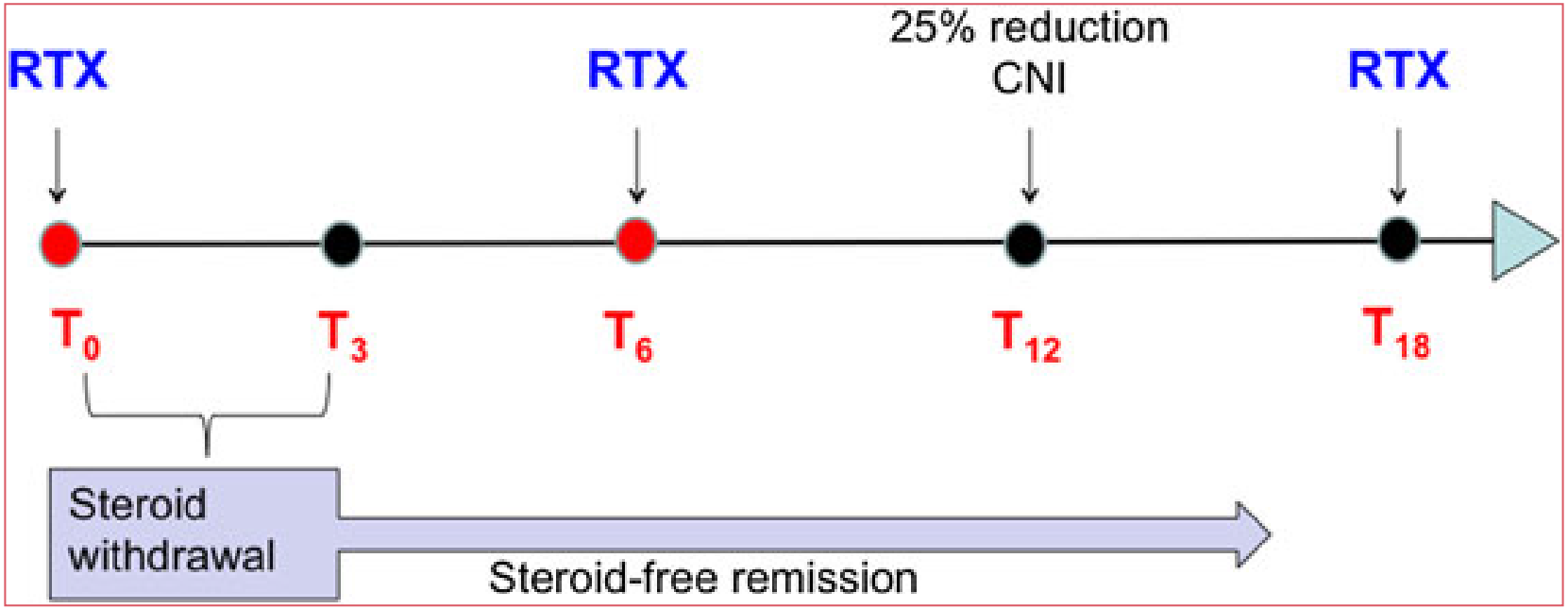
FRNS/SDNS: Rituximab in adults?

- Rituximab is effective in preventing relapses in children with FRNS/SDNS
- Limited data in adult patients
- No controlled trials in adult patients

- Prospective study in 15 adults
- MCD with FRNS or SDNS
- In remission with calcineurin inhibitor

Papakrivopoulou Nephrology 2016; 21: 893 - 900

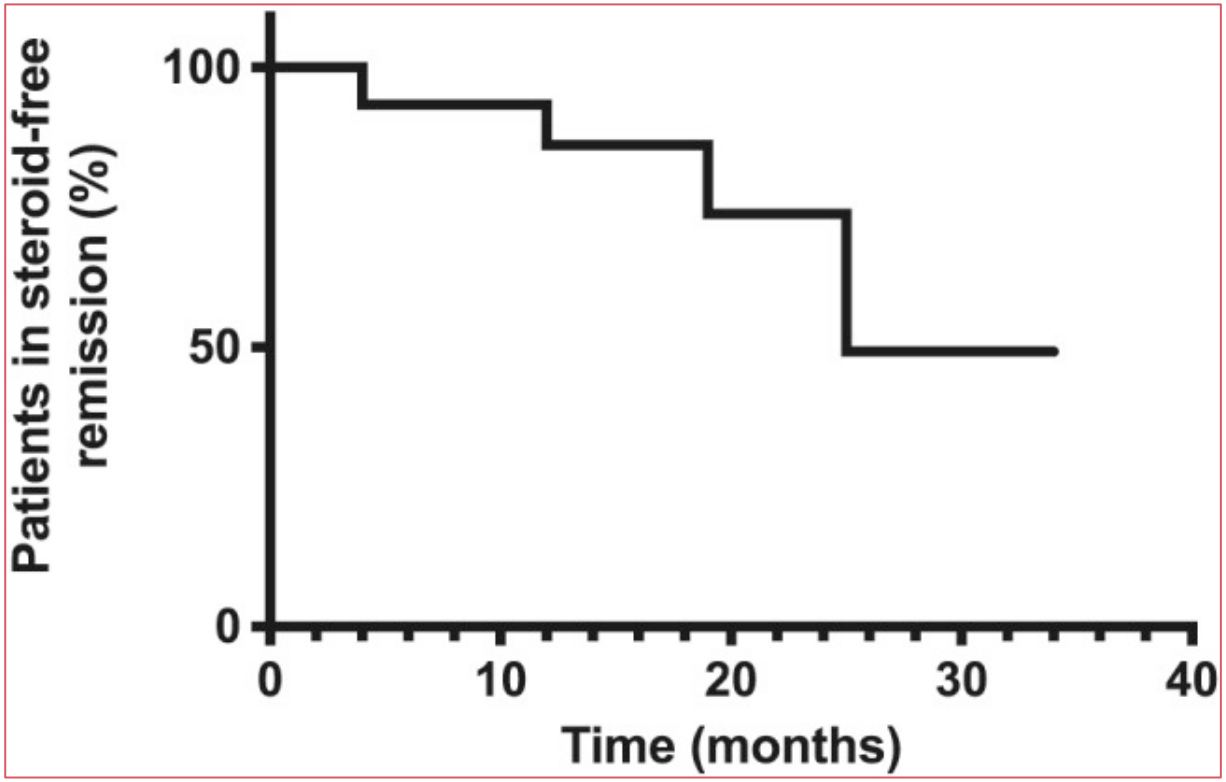
FRNS/SDNS: Rituximab in adults?
Treatment protocol



RITUXIMAB: Rituximab 1 gr; 1 dose (n=15), 2 doses (n=12), 3 doses (n=4)

Papakrivopoulou Nephrology 2016; 21: 893 - 900

FRNS/SDNS: Rituximab in adults? Results



Steroid-free remission: overall 25 months
1 dose: 12 months; 2 doses: 17 months; 3 doses: 27 months

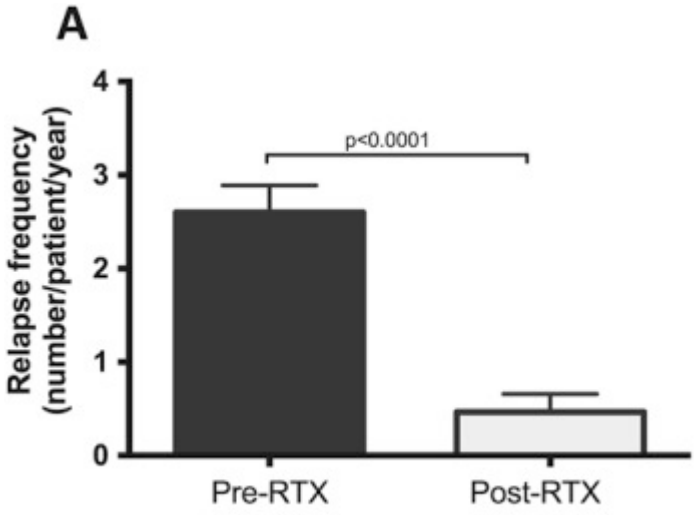
Papakrivopoulou Nephrology 2016; 21: 893 - 900

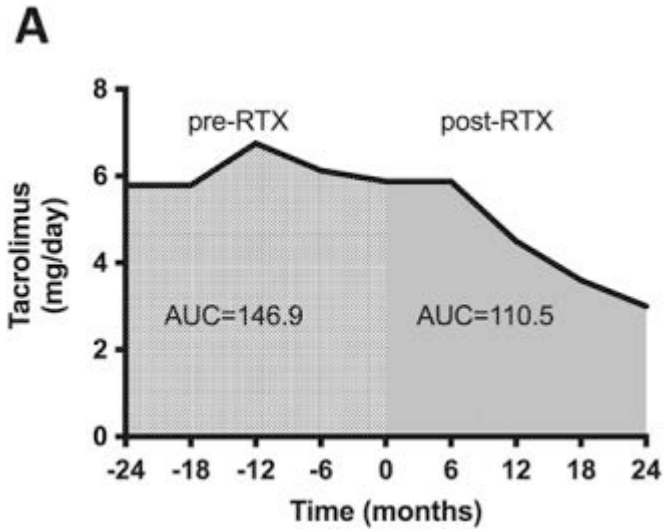
FRNS/SDNS: Rituximab in adults?

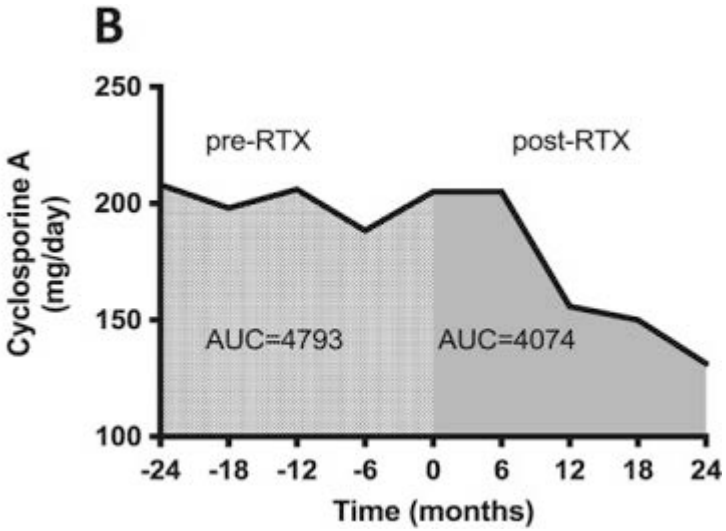
Fewer remissions with Rituximab

Patients continued CNI (in lower dose)

Treatment duration and monitoring?







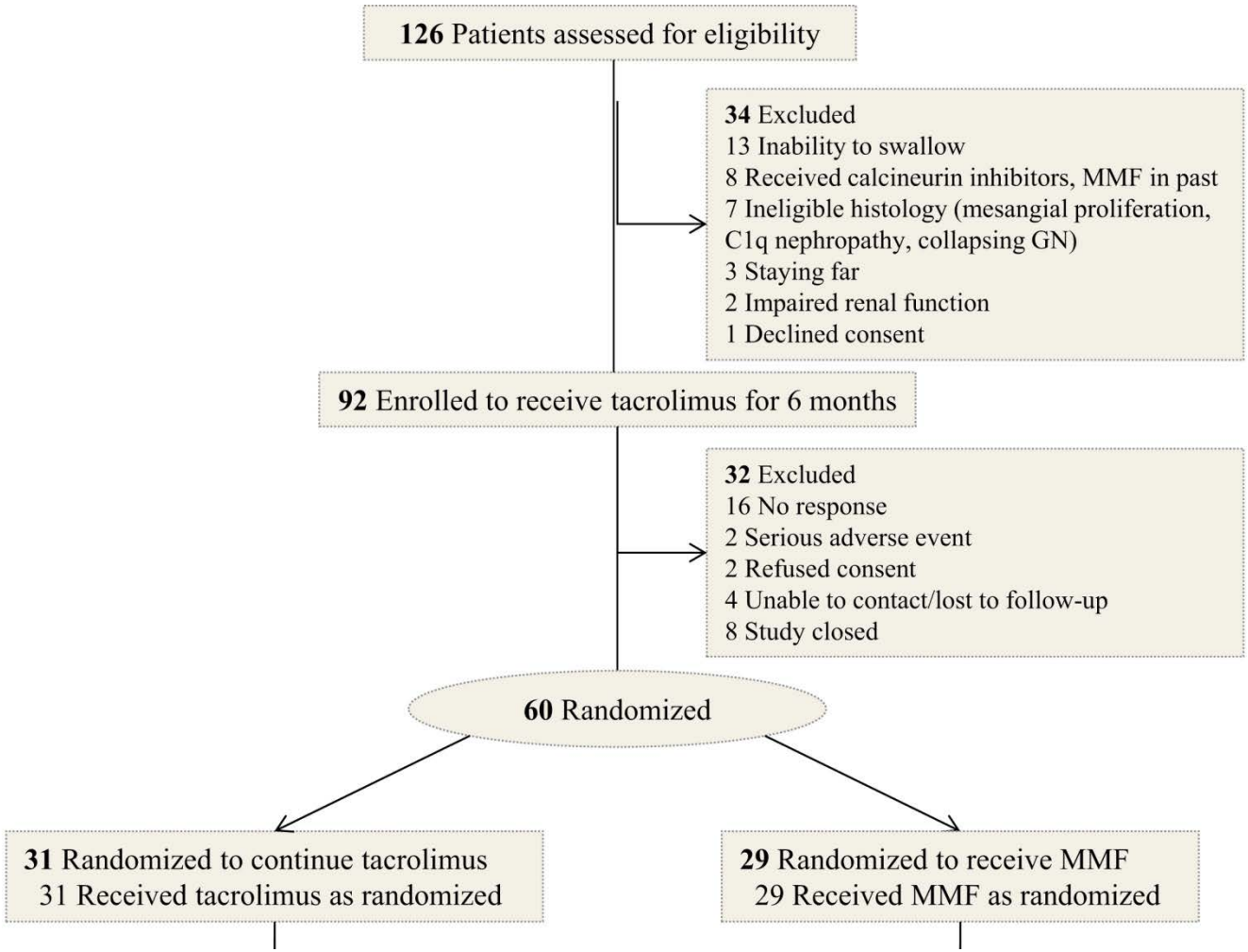
Papakrivopoulou Nephrology 2016; 21: 893 - 900

FSGS: steroid-resistant nephrotic syndrome

mycophenolate mofetil is inferior to tacrolimus in sustaining remission in children with idiopathic steroid-resistant nephrotic syndrome

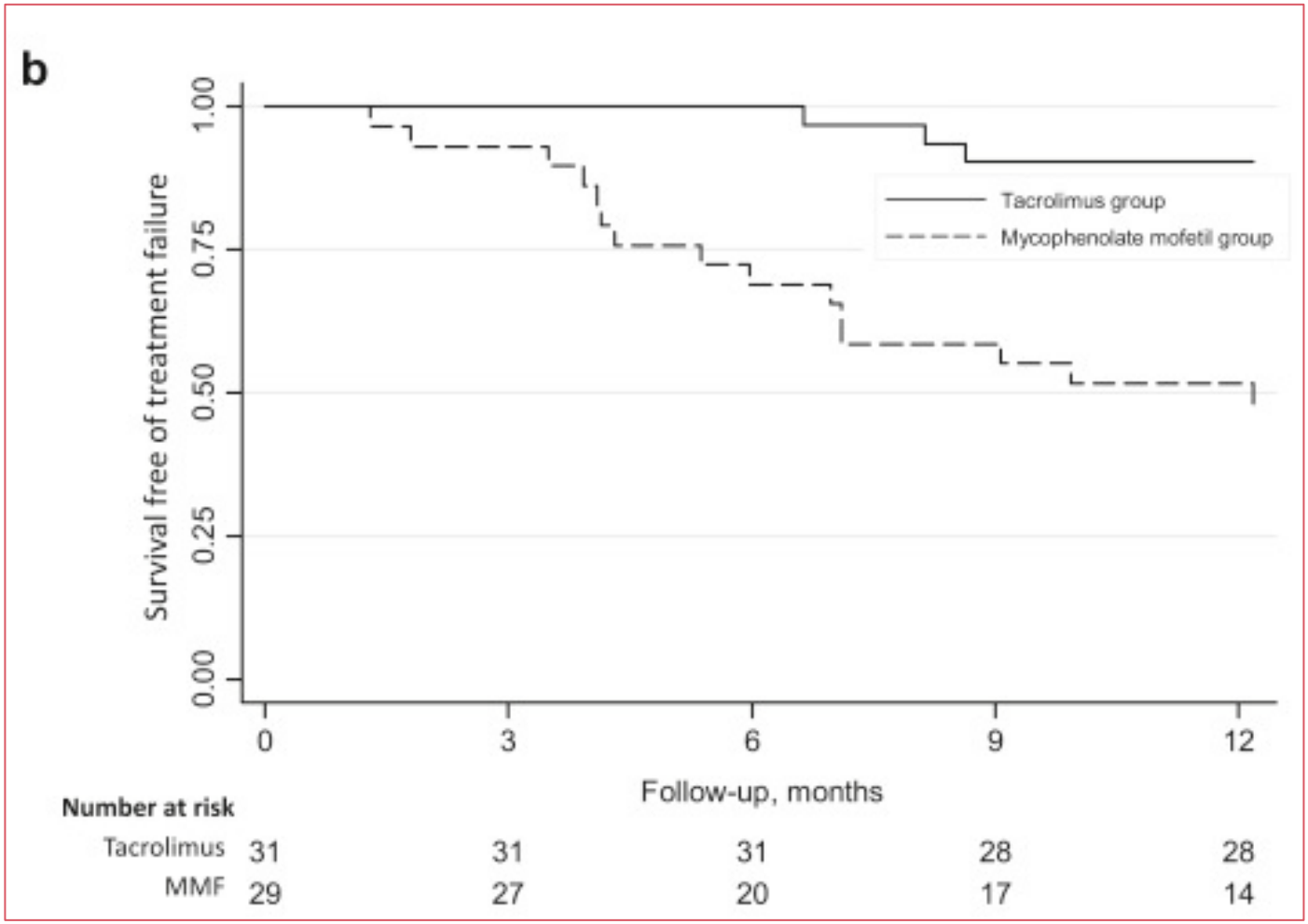
Sinha A et al. Kidney Int 2017; 92: 248-257

FSGS: steroid-resistant nephrotic syndrome



Sinha A et al. Kidney Int 2017; 92: 248-257

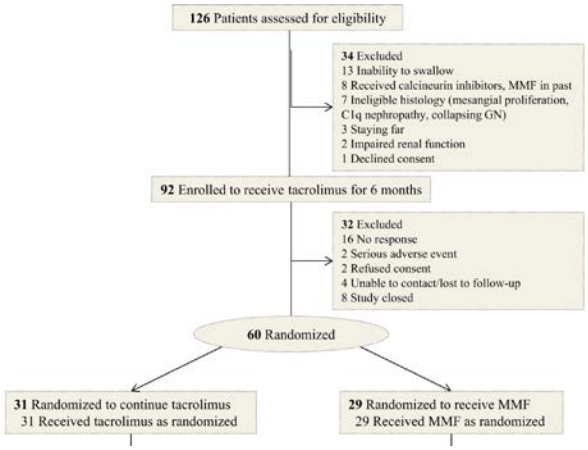
FSGS: steroid-resistant nephrotic syndrome



Treatment failure: prednisone-resistant relapse; frequent relapses; increase Screat

Sinha A et al. Kidney Int 2017; 92: 248-257

FSGS: steroid-resistant nephrotic syndrome



16/76 patients did not respond to tacrolimus!

Definition: SRNS
Nephrotic range proteinuria after 8 week prednisone:
4 weeks 2 mg/kg/day
4 weeks 1.5 mg/kg/48 hrs

Tacrolimus treatment:

Tacrolimus 0.1-0.15 mg/kg/day (Target levels: 4-7 ng/ml)

Prednisone: 1.5 mg/kg/48 hrs , tapering with 0.25 mg/kg every 4 weeks

Is this really STEROID RESISTANT?

Sinha A et al. Kidney Int 2017; 92: 248-257

FSGS: steroid resistant nephrotic syndrome

Continued treatment:

Tacrolimus: 0.10 – 0.15 mg/kg/day
+ prednisone 0.2-0.3 mg/kg/48 hrs

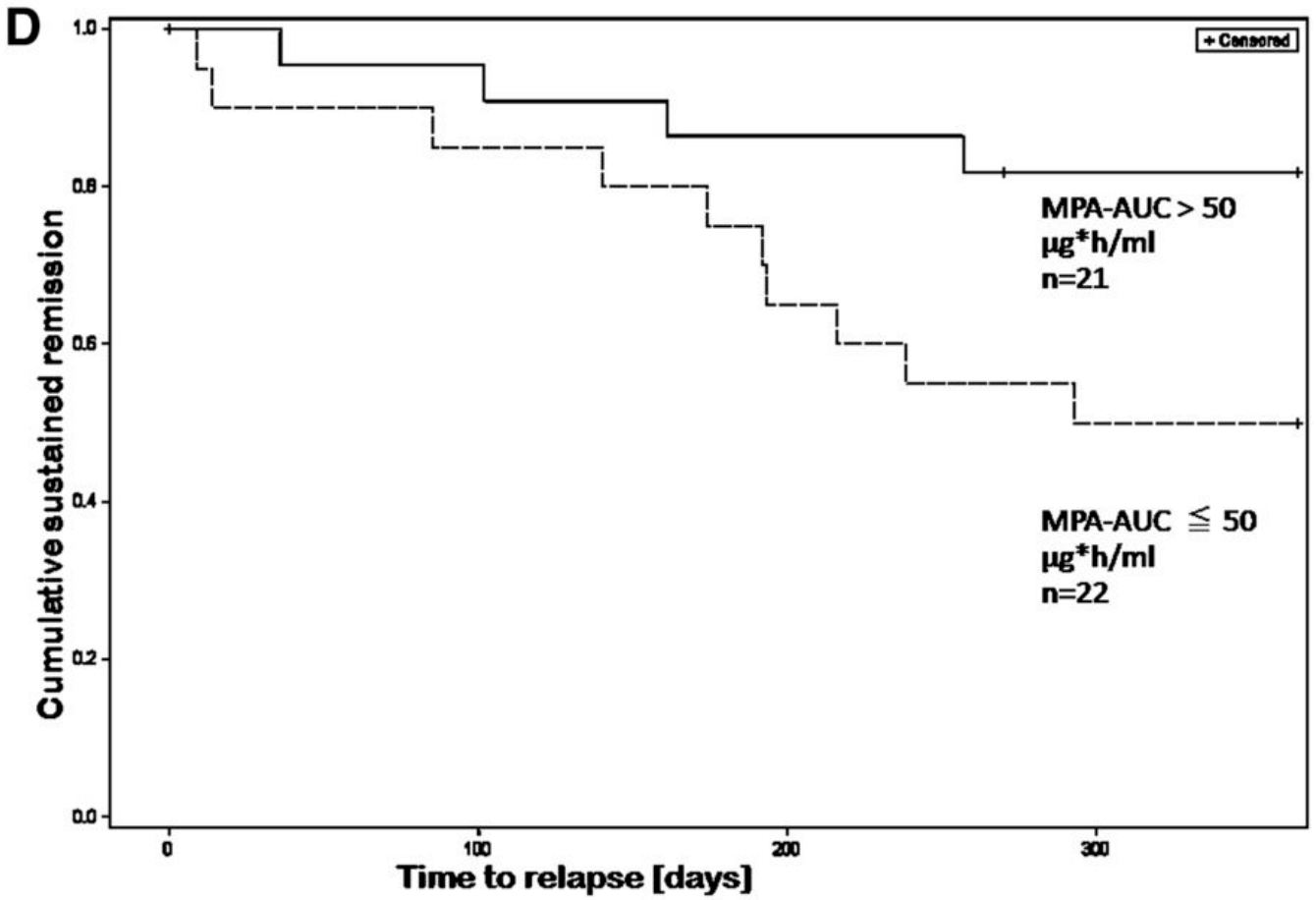
Therapeutic drug monitoring: target levels 4 – 7 ng/ml

MM F: 750-1000 mg/m2,
+ prednisone 0.2 -0.3 mg/kg/48 hrs

Therapeutic drug monitoring: no drug levels!

Sinha A et al. Kidney Int 2017; 92: 248-257

MYCOFENOLAAT MOFETIL: role of therapeutic drug monitoring



Jutta Gellermann et al. JASN 2013;24:1689-1697

MCD/FSGS: Take Home Message

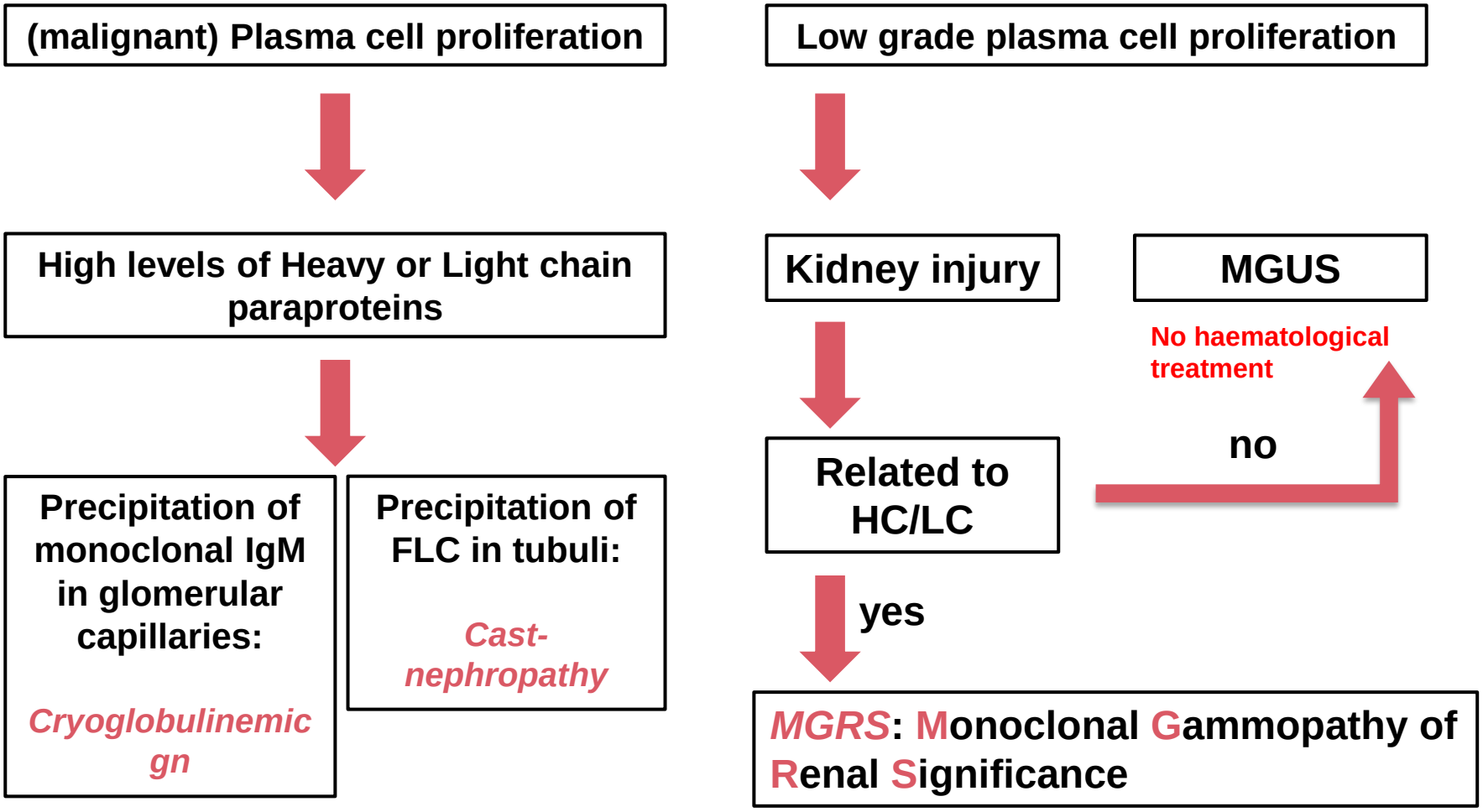
- In patients with MCD/FSGS and prednisone intolerance, tacrolimus monotherapy is a reasonable option (after induction with methylprednisolone i.v.)
- In patients with SRNS tacrolimus is effective
- Tacrolimus, target trough levels of 5 ug/l, is better than mycofenolate mofetil in maintaining remission
- The inferiority of mycofenolate mofetil may be related to insufficient drug levels. Consider measuring MMF-AUC If using mycofenolate mofetil
- Advise short course of prednisone during infectious episode in patients who recently stopped prednisone or are using a low dose

Glomerulonephritis: New entities: MGRS

Paraproteins and Kidney Disease: State of the Art

- Paraprotein associated kidney diseases:
  - Cast nephropathy
  - Amyloidosis
  - Light chain deposition disease

Paraproteins and kidney damage: new view



----------Haematological Treatment----------

Monoclonal Gammopathy of Renal Significance

It is not the load! Physicochemical properties or epitope specificity determine damage

Immunoglobin light chain Amyloidosis (AL)
Immunoglobin heavy chain Amyloidosis (AH)
Immunoglobin light and heavy chain Amyloidosis (AHL)
Fibrillary glomerulonephritis
Immunotactoid glomerulonephritis
Cryoglobulinemic glomerulonephritis
Toxic-tubulopathy + crystals
Toxic tubulopathy – crystals
Interstitial crystal storing histiocytosis
Light chain deposition disease
Heavy chain deposition disease
Light and Heavy Chain Deposition Disease
PGNMID (Proliferative gn with monoclonal immune deposits)
Paraprotein-associated membranous nephropathy with masked IgGk deposits
Paraprotein associated C3GN
Paraprotein associated TMA
Crystalglobulin-associated nephropathy
Light chain podocytopathy

Monoclonal Gammopathy of Renal Significance

Description:

Glomerular/tubular

Organized/non-organized

A search for paraproteins

Serum IEF/immunofixation
urine IEF/ immunofixation
Serum Free light Chains

Kidney Biopsy
LM
IF: paraproteins?
EM

No technique is 100% accurate!
Pronase digestion needed?!

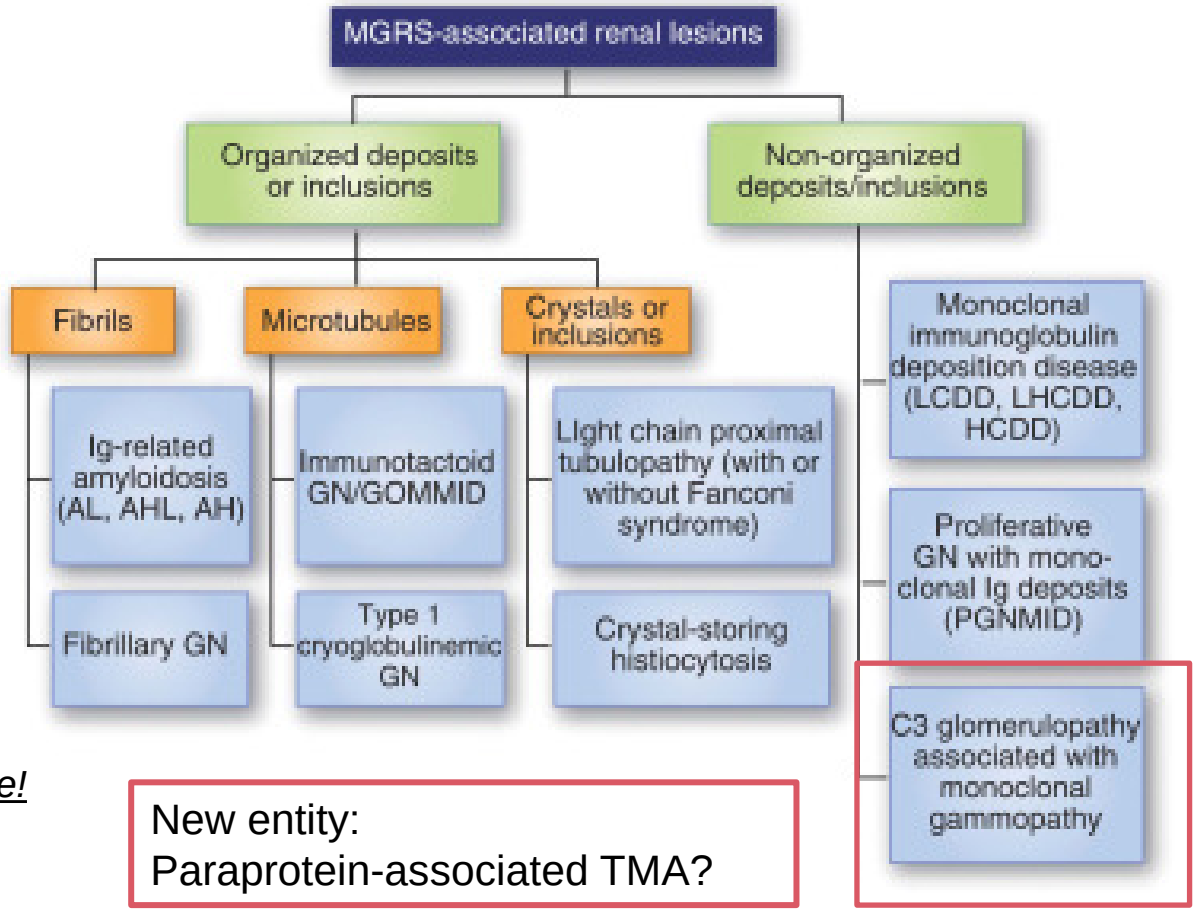


Figure 2. Diagram of MGRS-associated renal lesions. AH, immunoglobulin heavy chain amyloidosis; AHL, immunoglobulin heavy and light chain amyloidosis; AL, immunoglobulin light chain amyloidosis; GN, glomerulonephritis; GOMMID glomerulonephritis with organized microtubular monoclonal immune deposits

Bridoux F et al. Kidney International 2015; 87: 698 - 711

Monoclonal Gammopathy of Renal Significance:

Accuracy of diagnostic tests

False negative:

IF biopsy: proteins are degraded and loose epitopes;

IEF serum/urine: do not detect low concentrations

FLC: negative in Heavy Chain only disease; can be negative in amyloidosis

False positive:

MGUS (Is there MGUS in a patient with MG and kidney damage?)

Monoclonal Gammopathy of Renal Significance:

Accuracy of diagnostic tests

False negative:

IF biopsy: proteins are degraded and loose epitopes; (or paraprotein does not cause local damage)

IEF serum/urine: do not detect low concentrations

FLC: negative in Heavy Chain only disease; can be negative in amyloidosis

False positive:

MGUS (Is there MGUS in a patient with MG and kidney damage?)

Monoclonal Gammopathy of Renal Significance: What is new?

Paraprotein associated TMA

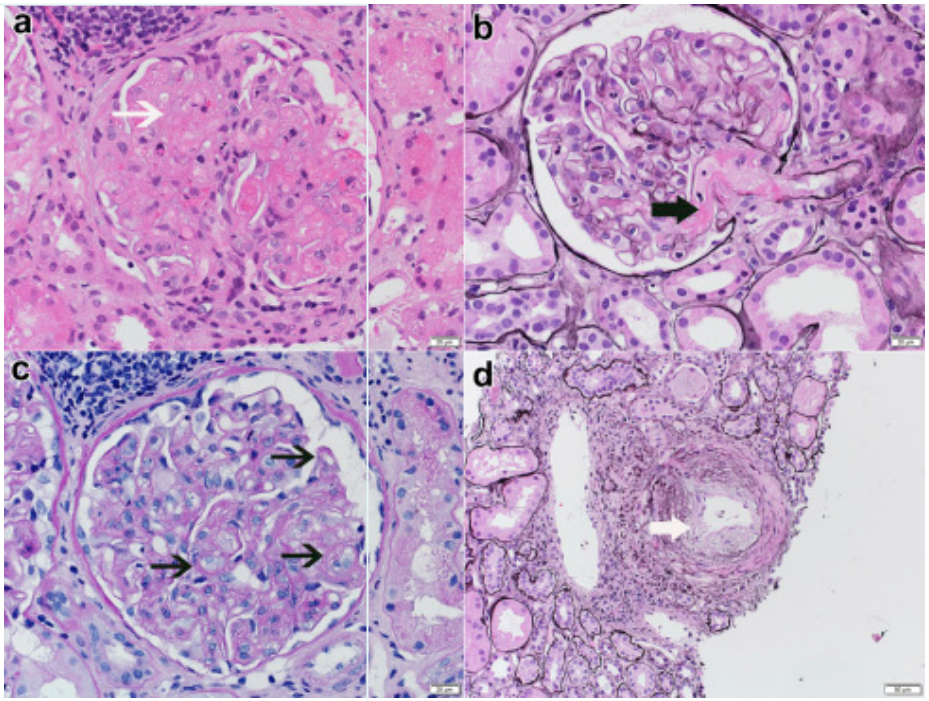
146 patients with TMA
20 (13.7%) with paraprotein
15 MGUS

Incidence of paraprotein:
4* higher than expected

Biopsy: negative!

Biopsy: 5/15 no thrombi!

Another form of MGRS? Test for paraprotein in specific types of kidney damage!?



Ravindran et al. Kidney International 2017; 91: 691 - 700

MGRS: Take Home Message

- **Variable presentation**
- **Many diagnostic tools, often only circumstantial evidence**
- **The presence of a paraprotein should lead to consider MGRS**

(or cast-nephropathy if overt Bence Jones proteinuria)

- **The presence of a paraprotein does not proof MGRS**
- **The absence of a paraprotein in serum, urine, or kidney tissue**

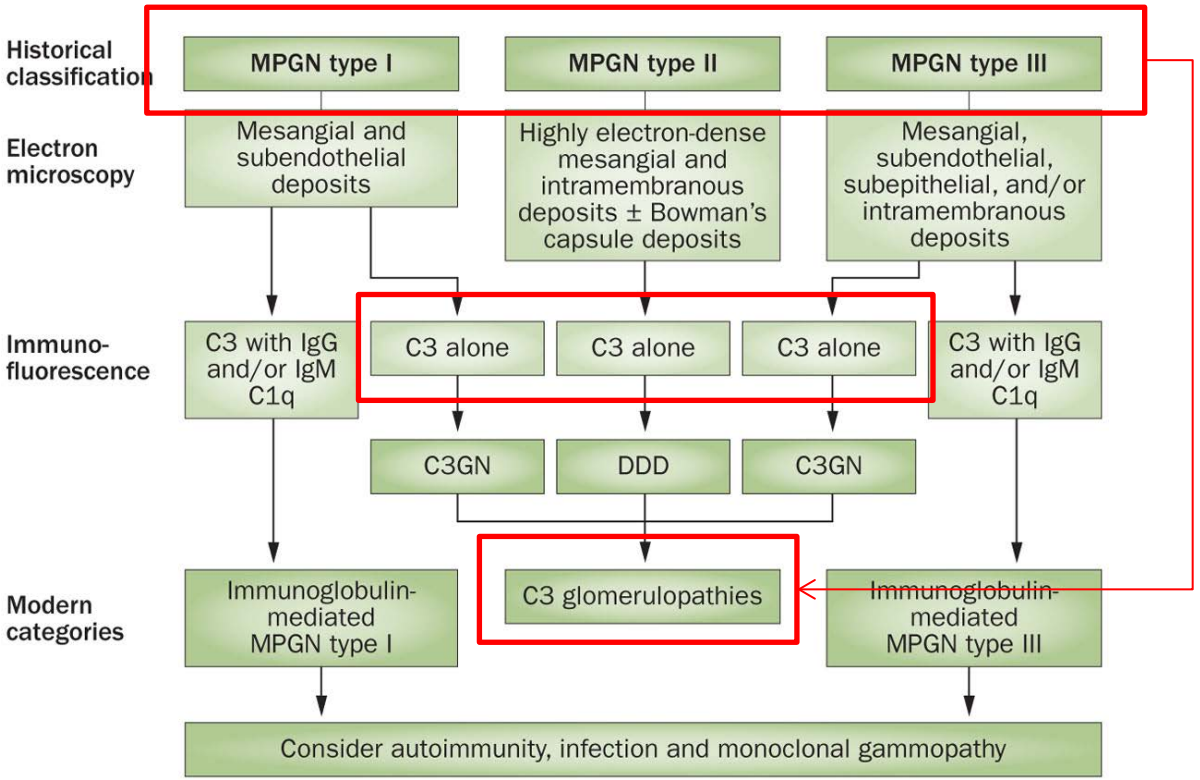
does not exclude MGRS

- **Always consider paraprotein as cause of “unexplained” kidney**

disease

Paraproteins and C3 Nephropathy

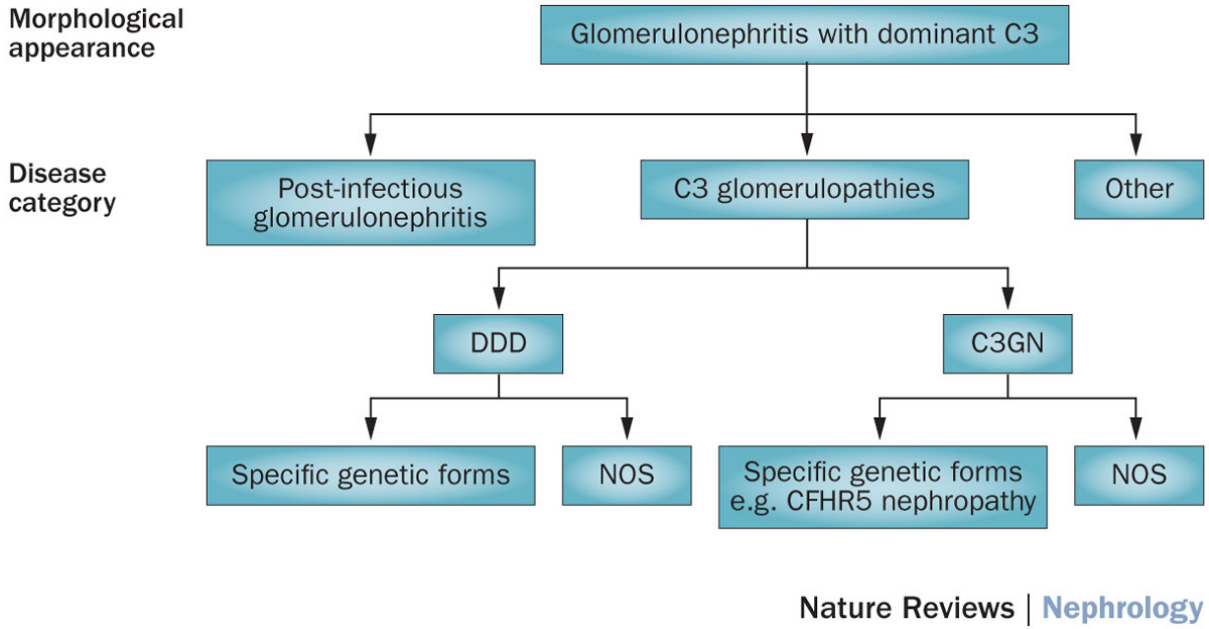
The relationship between historical and modern classification of glomerulonephritis with membranoproliferative morphology



Cook, H. T. & Pickering, M. C. (2014) Histopathology of MPGN and C3 glomerulopathies Nat. Rev. Nephrol. doi:10.1038/nrneph.2014.217

Paraproteins and C3 Nephropathy

- C3 glomerulonephritis: **dominant** C3 (≥ 2+ vs IgG)



Cook, H. T. & Pickering, M. C. (2014) Histopathology of MPGN and C3 glomerulopathies Nat. Rev. Nephrol. doi:10.1038/nrneph.2014.217

Paraproteins and C3 Nephropathy

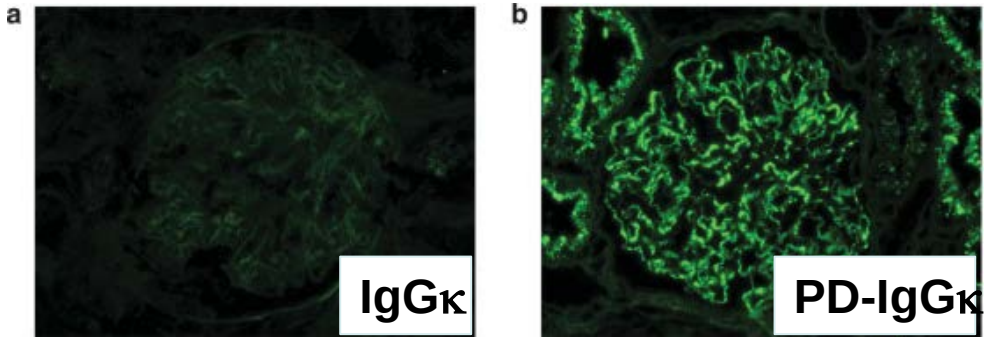
- C3 glomerulonephritis: dominant C3 (≥ 2+ vs IgG)

Disorder	Symptoms	LM	IF	EM	Serum Urine
C3 glomerulopathy with monoclonal gammopathy	Proteinuria NS Hematuria CKD	MPGN MesP gn Endocapillary gn	Granular C3 **No Ig**	Intramembranous dense deposits (DDD) Subendothelial and mesangial deposits (C3N)	sIEF 100% FLC 75-100%

Frank Bridoux, et al
Kidney International, Volume 87, Issue 4, 2015, 698–711

Monoclonal Gammopathy of Renal Significance: What is new?

Membranous-like glomerulopathy with masked IgG kappa deposits



1. **Paraproteins may be absent in routine IF → detectable after pronase**
2. **Paraproteins may affect systemic complement and therefore may be absent anyway.**

Larsen C et al. Kidney International 2014: 86: 154 - 161

C3 Nephropathy: Take Home Message

- C3 glomerulonephritis: “new” disease
- Requires thorough investigation

- Infections?
- Complement abnormalities?
- Paraproteins?

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List of Abbreviations

- NIAT: non-immunosuppressive antiproteinuric therapy
- RC: randomized controlled trial
- SAE: serious adverse event
- ST-CP: steroid-cyclophosphamide
- RTX: rituximab
- RPGN: rapidly progressive glomerulonephritis
- ACEi Angiotensin Converting Enzyme Inhibitor
- ARB Angiotensin Receptor Blocker
- TRF Targeted Release Formula
- RR Blood Pressure
- UPCR Urine Protein Creatinine Ratio
- ESRD End Stage Renal Disease
- MCD Minimal Change Disease
- FSGS Focal Segmental Glomerulosclerosis
- FRNS Frequently Relapsing Nephrotic Syndrome
- SDNS Steroid-dependent Nephrotic Syndrome
- SRNS Steroid resistant Nephrotic Syndrome
- CNI Calcineurin Inhibitor
- AUC Area under the Curve
- GPA Granulomatous Polyangiitis
- MPA Microscopic Polyangiitis
- EGPA Eosinophilic granulomatous Polyangitis
- SLE Systemic Lupus Erythematodes
- LN Lupus nephritis
- AZA Azathioprine
- IVCY Intravenous Cyclophosphamide

IEF	Immunoelectrophoresis
LM	light microscopy
IF	Immunofluorescence
EM	Electronmicroscopy
TMA	Thrombotic microangiopathy
FLC	Free light chains
MGRS	Monoclonal gammopathy of renal significance
MGUS	Monoclonal gammopathy of undetermined significance