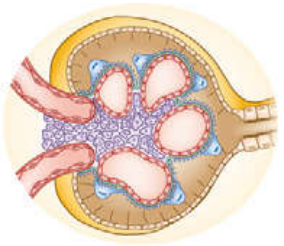
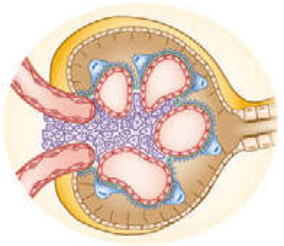


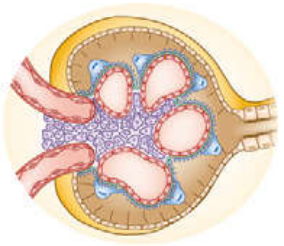
CNIs in the treatment of membranous nephropathy

Esmat abdollahpour, MD, assistant professor, nephrology ward, shariati hospital, TUMS

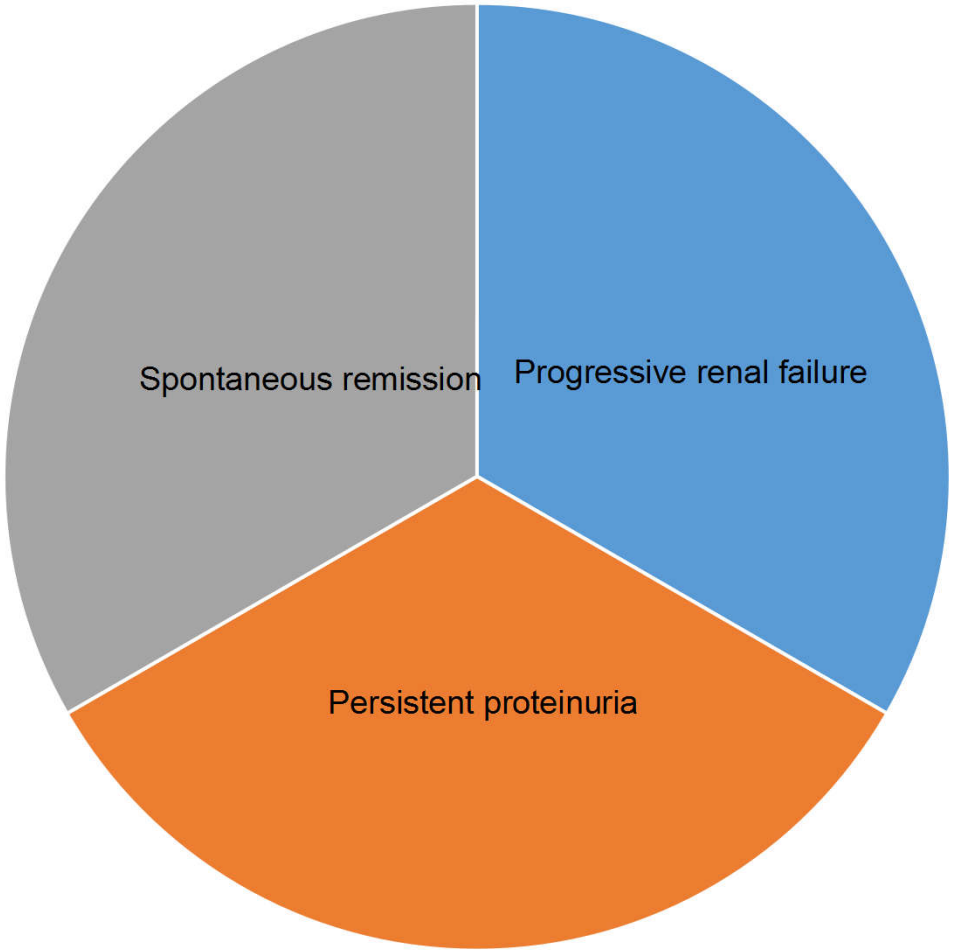


Trends in Toronto Glomerulonephritis Registry: 1975–2015

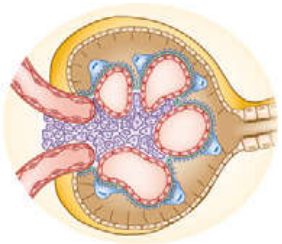
	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2011	2012–2015[a]	Total
MN	134	172	171	164	129	138	230	168	1306
MPGN	99	67	33	46	37	22	34	N/A	329
FSGS	141	164	163	239	311	318	338	288	1962
IGA	129	215	227	262	309	299	349	286	2076
LUPUS	170	191	143	174	136	130	262	N/A	1206
Vasculitis	29	66	76	93	76	87	152	N/A	579

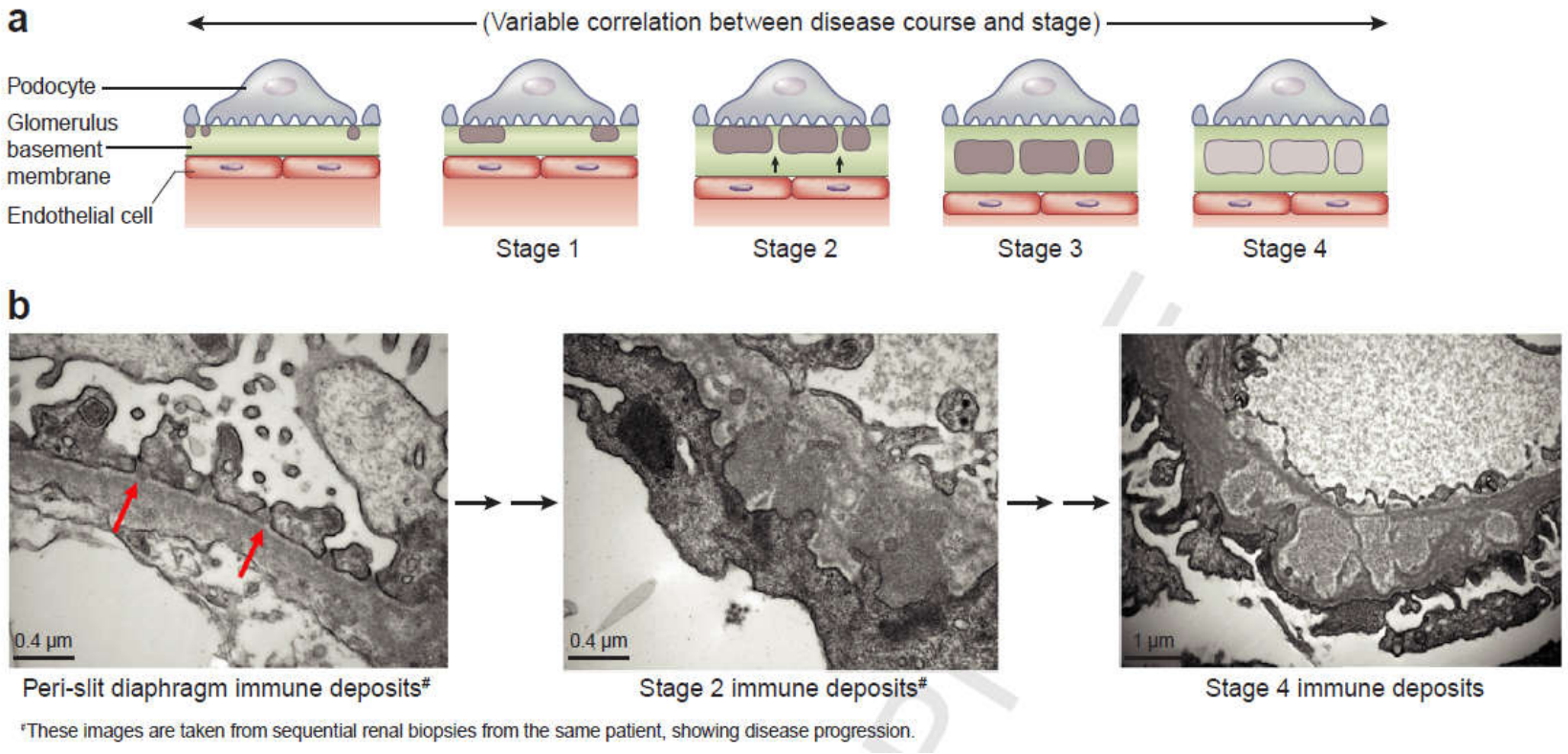


Natural history



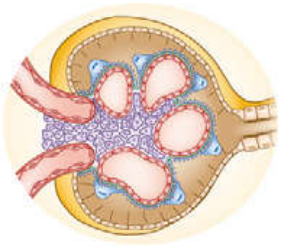
Rule of thirds





- Schematic depiction of the primary membranous nephropathy stages with representative electron microscopy (EM) images of select stages
- The immune deposits consist of immunoglobulin (Ig) G, the relevant antigens, and the membrane attack complex of complement

Kidney International (2021)



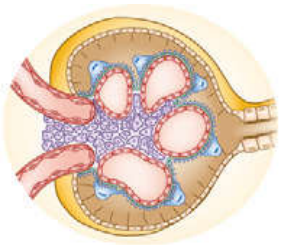
Animal model of antigen, Heymann nephritis (megalin) 1959

NEP 2002

PLA2R 2009

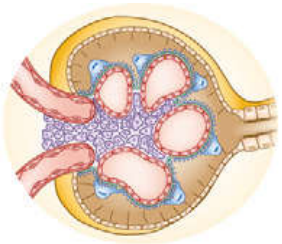
THSD7A 2014

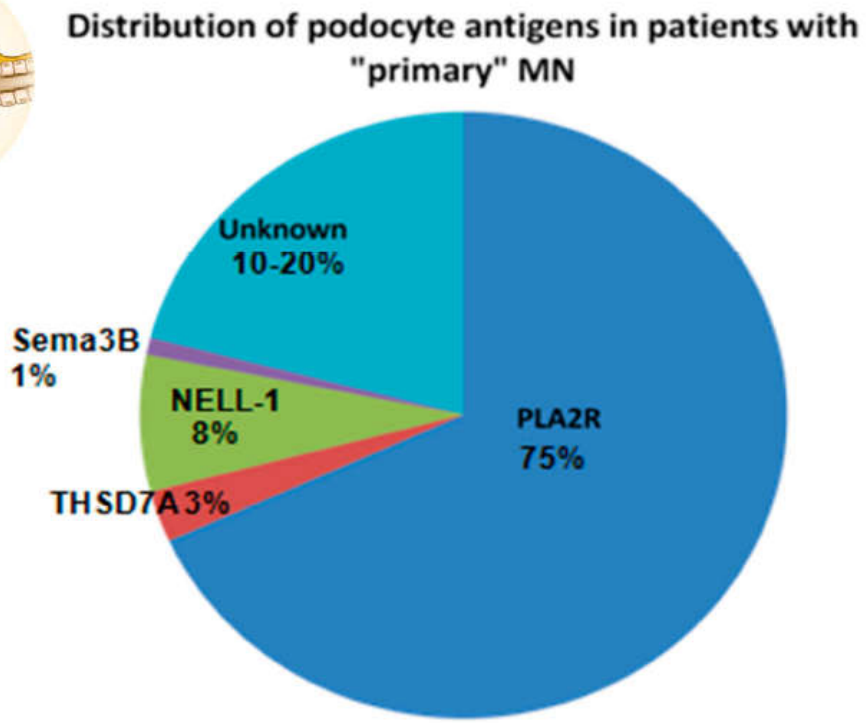
Mass spectrometry era (NELL-1, Sema3B, …), 2019→ ???



Probability Legend: over 95% / 80% to 94% / 50% to 79% / 20% to 49% / 0% to 19% Bio View: 2071 Proteins in 1869 Clusters With 2070 Filtered Out	Accession Number	Molecular Weight	Protein Grouping Ambiguity	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Secretory phospholipase A2 receptor OS=Homo sapiens OX=9606 GN=PLA2R1 PE=1 SV=2	sp|Q13018|PLA2R_HUMAN	169 kDa	★	75	6	8	10	6	4
Thrombospondin type-1 domain-containing protein 7A OS=Homo sapiens OX=9606 GN=TH...	sp|Q9UPZ6|THS7A_HUMAN	185 kDa	★	4	47	(0)	3	1	3
Exostosin-1 OS=Homo sapiens OX=9606 GN=EXT1 PE=1 SV=2	sp|Q16394|EXT1_HUMAN	86 kDa	★	(0)	(0)	64	(0)	(0)	(0)
Exostosin-2 OS=Homo sapiens OX=9606 GN=EXT2 PE=1 SV=1	sp|Q93063|EXT2_HUMAN	82 kDa		(0)	(0)	85	(0)	(0)	(0)
Protein kinase C-binding protein NELL1 OS=Homo sapiens OX=9606 GN=NELL1 PE=1 SV=4	sp|Q92832|NELL1_HUMAN	90 kDa		(0)	(0)	(0)	58	(0)	(0)
Semaphorin-3B OS=Homo sapiens OX=9606 GN=SEMA3B PE=2 SV=1	sp|Q13214|SEM3B_HUMAN	83 kDa		(0)	(0)	(0)	(0)	53	(0)
Protocadherin-7 OS=Homo sapiens OX=9606 GN=PCDH7 PE=1 SV=2	sp|O60245|PCDH7_HUMAN	116 kDa		(0)	(0)	(0)	(0)	0	23

Figure 4. Representative mass spectrometry and detection of antigens in MN. Case 1 is from a biopsy specimen of PLA2R-associated MN, case 2 from THSD7A-associated MN, case 3 from EXT1/EXT2-associated MN, case 4 from NELL1-associated MN, case 5 from Sema3B-associated MN, and case 6 from PCDH7-associated MN. Numbers in green boxes represent spectral counts of MS/MS matches to a respective protein. Red star indicates shared amino acid sequences among proteins.





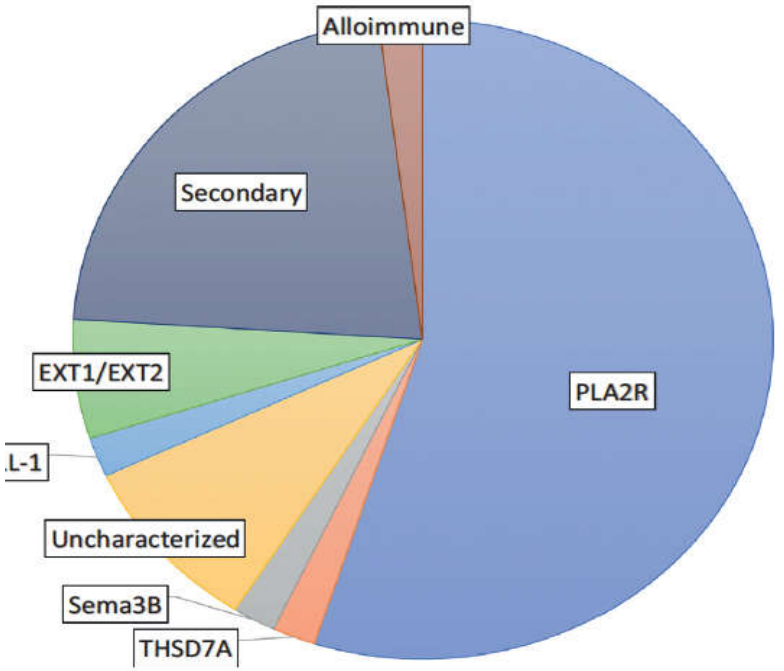
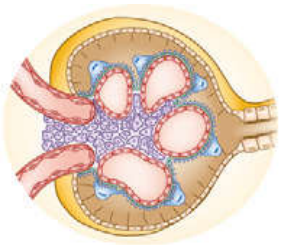
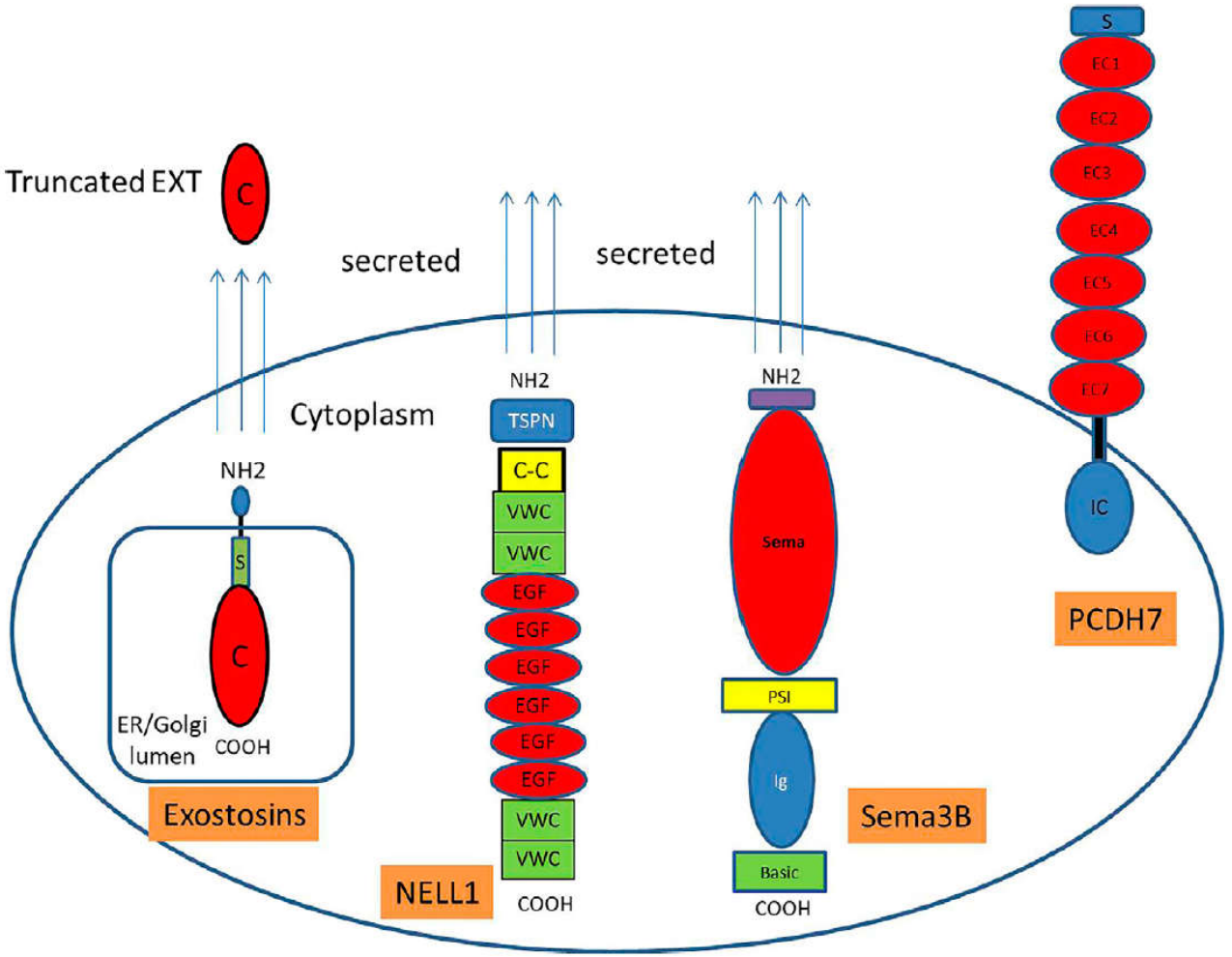


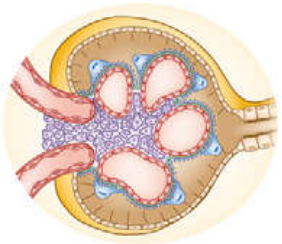
Figure 1. Spectrum of disease within the larger pathologic classification of MN according to the observation that secondary entities represent approximately 30% of all MN. The percentages of MN associated with the newer antigens NELL-1, Sema3B, and EXT1/EXT2 are estimates, and larger cohorts are needed to determine the true prevalence of these subtypes of MN. The uncharacterized group reflects those cases of presumed primary MN in which the target antigen has yet to be described.

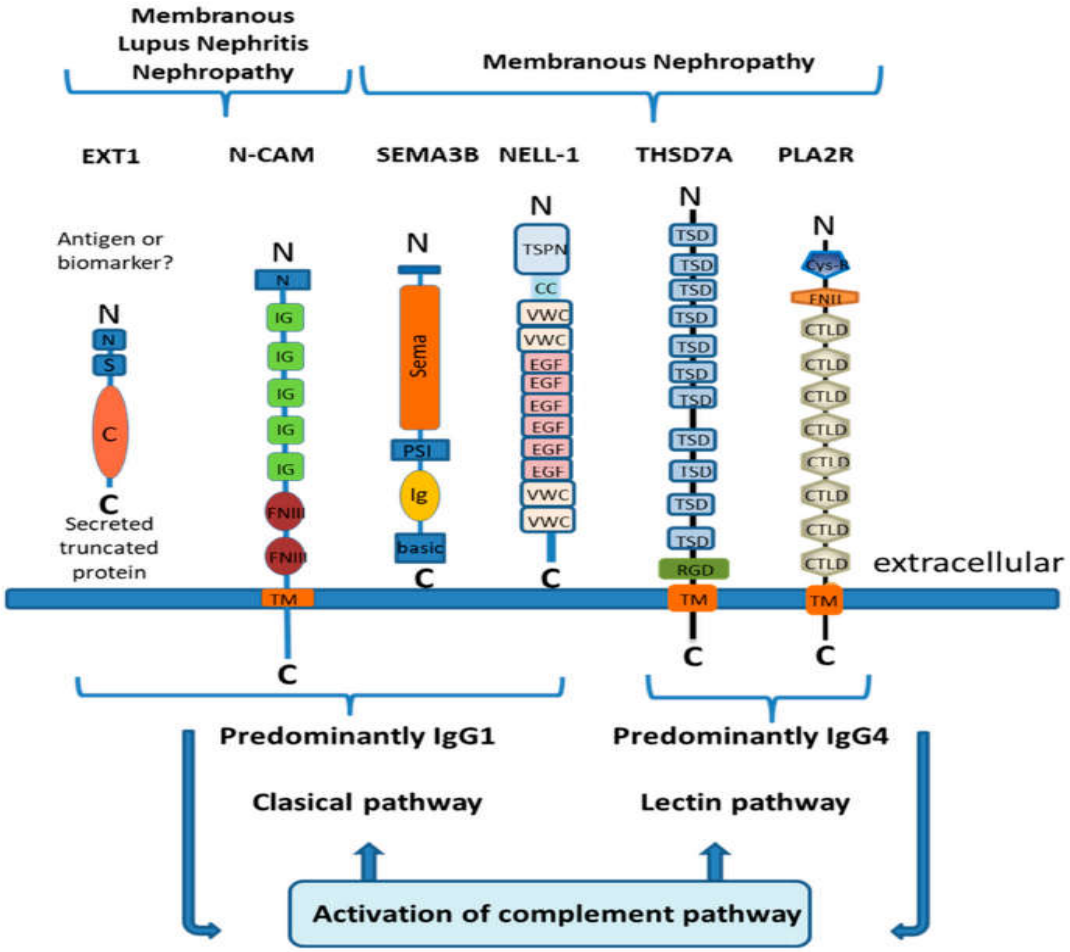




Schematic representation of the MN proteins

JASN 32: 268–278, 2021

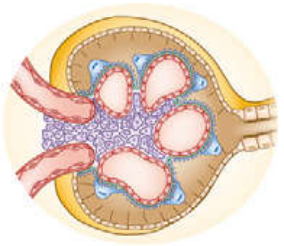




1. protocadherin-7 (PCDH7)
2. High temperature recombinant protein A1 (HTRA1)

Antigens of membranous nephropathy and their schematic molecular structure

J. Clin. Med. **2021**, 10, 607



Clinical and pathologic findings

Table 1. Clinical and pathologic findings

MN	Mean Age (yr)	Sex (M:F)	Laboratory Findings	Disease Association	Serum Antibody	LM	IF	Complement	IgG Subtype	EM
EXT1/EXT2-MN (n=26)	36	1:4	ANA, dsDNA, SSA, SSB, others	Autoimmune diseases: lupus, MCTD/	No	Proliferative features may be present	IgG, IgA/IgM	C3, C1q	IgG1	SE, ME + SU +/− TRI
NELL1-MN (n=34)	63	1:1	Negative	Malignancy	Yes (nonreducing)	Nonproliferative	IgG	C3	IgG1	SE, segmental deposits
Sema3B-MN (n=11)	7[a]; 36[b]	6:4	Negative	Family history	Yes	Nonproliferative	IgG, TBM +	C3	IgG1	SE, TRI, TBM +
PCDH7-MN (n=10)	61	3:1	Negative	None	Yes	Nonproliferative	IgG	−/Trace	IgG1, IgG4	SE

The numbers in parenthesis represent the total patients with each specific type of MN that were part of the original studies. M, male; F, female; LM, light microscopy; EM, electron microscopy; ANA, anti-nuclear antibody; dsDNA, double-stranded DNA; SSA, anti–Sjögren syndrome–related antigen A; SSB, anti–Sjögren syndrome–related antigen B; MCTD, mixed connective tissue disease; SE, subepithelial; ME, mesangial; SU, subendothelial; TRI, tubuloreticular inclusions.

[a]Age in children.

[b]Age in young adults.

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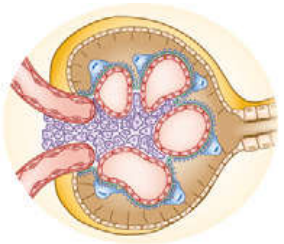
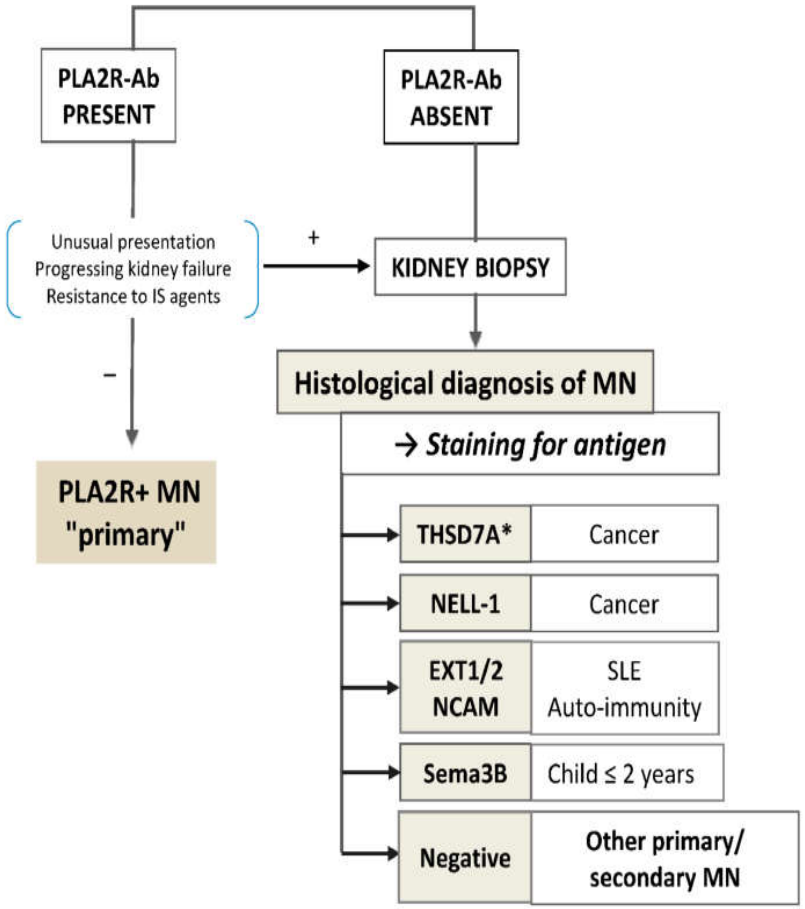
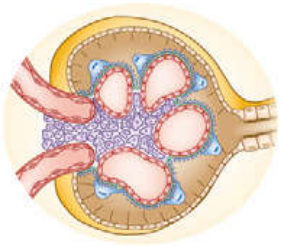




Simplified diagnostic algorithm

PCDH7-associated MN had an associated prostate carcinoma. PCDH7 is mostly present in older patients.

J. Clin. Med. **2021**, 10, 607



Cumulative incidence of ESKD in patients with lupus membranous nephritis (LMN).

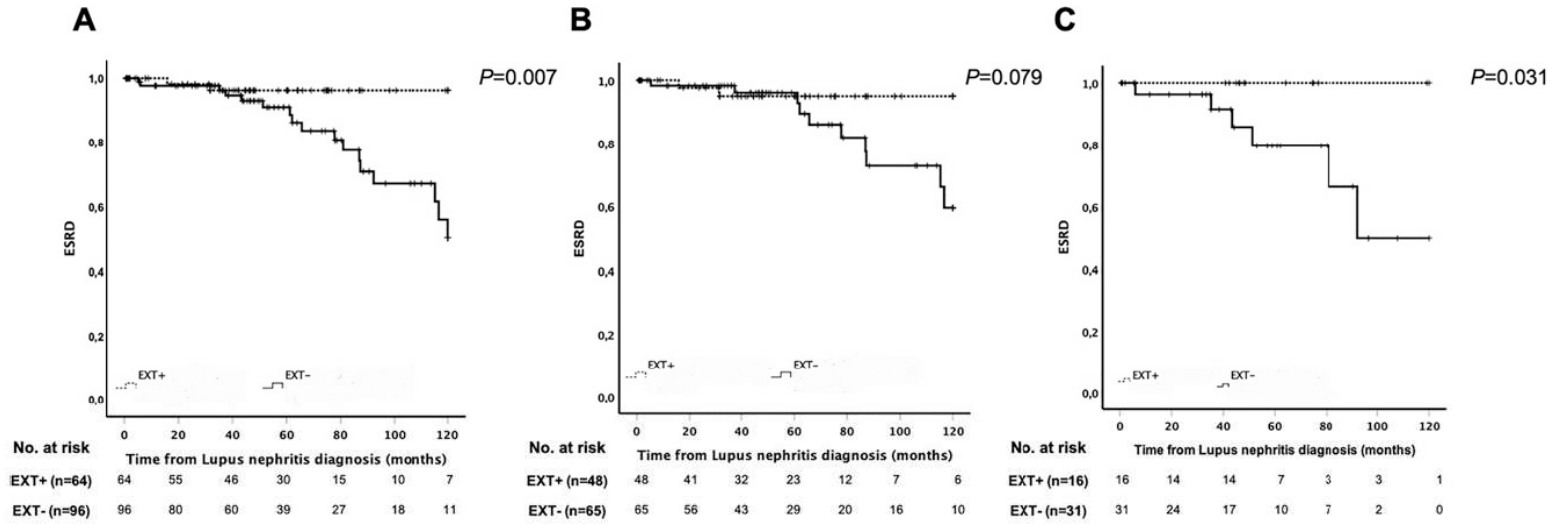


Figure 3. Cumulative incidence of ESKD in patients with lupus membranous nephritis (LMN). Kaplan–Meier plots of the cumulative incidence of ESKD over 10 years. (A) EXT1/EXT2-positive and EXT1/EXT2-negative LMN (including class III/IV lupus nephritis [LN]): 64 EXT+ versus 96 EXT−; two versus 18 events; time to event, 116 versus 101 months; $P=0.007$. (B) EXT1/EXT2-positive and EXT1/EXT2-negative pure class V LMN (with no class III/IV LN): 48 EXT+ versus 65 EXT−; two versus 11 events; time to event, 115 versus 104 months; $P=0.08$. (C) EXT1/EXT2-positive and EXT1/EXT2-negative class V LMN + class III/IV LN: 16 EXT+ versus 31 EXT−; zero versus seven events; time to event in EXT−, 96 months; $P=0.03$. EXT1/EXT-positive represented by dotted lines and EXT1/EXT2-negative represented by solid lines. Plots courtesy of Dr. Aishwarya Ravindran and Dr. Marta C. Moura.

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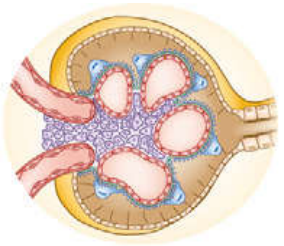
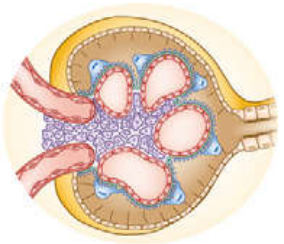


Primary MN

Secondary MN

Alloimmune MN



Box 1. Common Causes of Primary, Secondary, or Alloimmune MN

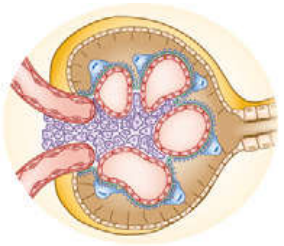
Primary MN[a]
- PLA_2R-associated
- THSD7A-associated
- NELL-1–associated
- Sema3B-associated
- Uncharacterized

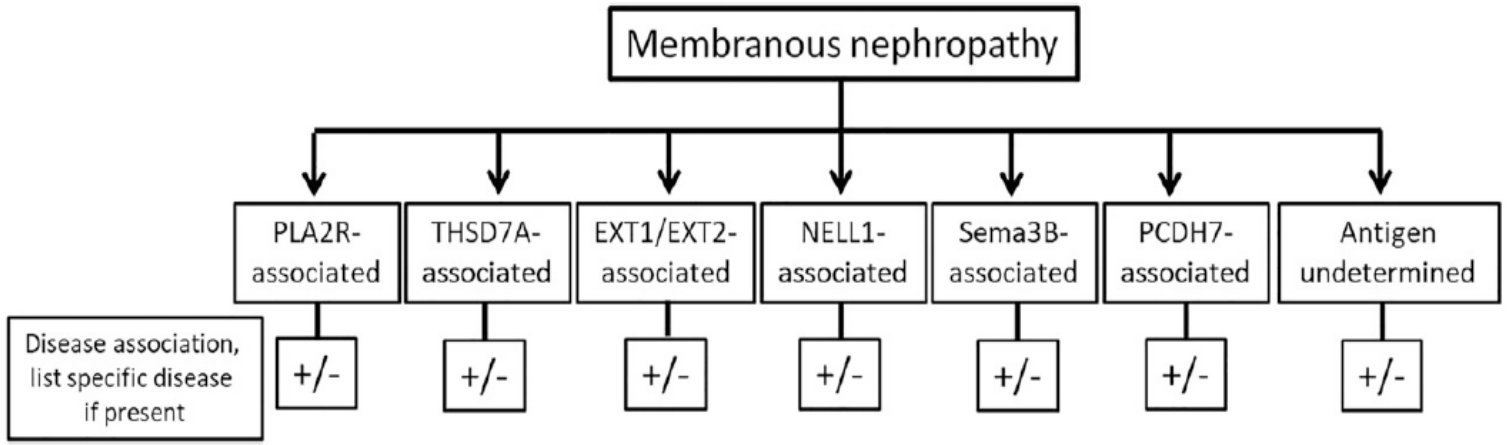
Secondary MN
- Autoimmune/collagen-vascular disease: SLE and mixed connective tissue disease (includes EXT1/EXT2-associated), Sjogren's, thyroiditis, sarcoidosis, dermatitis herpetiformis
- Infection: HBV and HCV, malaria, secondary or congenital syphilis, leprosy
- Drugs, toxins, other adulterants: NSAIDs, gold salts, penicillamine, mercury, cationic bovine serum albumin (infant formula)
- Malignancy: more commonly solid-organ carcinomas (lung, breast, colon, and kidney), NHL, leukemia; rarely associated with THSD7A expression in tumor; NELL-1–associated MN linked to underlying malignancy

Alloimmune MN
- Antenatal alloimmune MN caused by anti-NEP antibodies
- De novo MN in kidney allograft
- Graft-vs-host disease

Abbreviations: EXT1/EXT2, Exostosin 1/Exostosin 2; HBV, hepatitis B virus; HCV, hepatitis C virus; MN, membranous nephropathy; NELL-1, neural epidermal growth factor-like 1; NEP, neutral endopeptidase; NHL, non-Hodgkin lymphoma; NSAID, nonsteroidal anti-inflammatory drug; PLA_2R, phospholipase A_2 receptor; Sema3B, semaphorin-3B; SLE, systemic lupus erythematosus; THSD7A, thrombospondin type 1 domain-containing 7A.

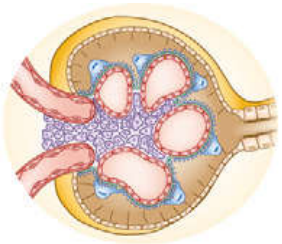
[a]Primary MN reflects an autoimmune process that targets an intrinsic podocyte protein (see text). NELL-1–associated MN is included here even though the source of the antigen is not yet clear. Several more target antigens are under investigation but are listed here as uncharacterized.





Proposed classification of MN.MN is classified on the basis of the antigen detected. In cases where none of the known antigens are detected, the terminology “undetermined” should be used. The disease association should be given if present, not present, or if not known.

JASN 32: 268–278, 2021



Schematic overview of the complement cascade in MN

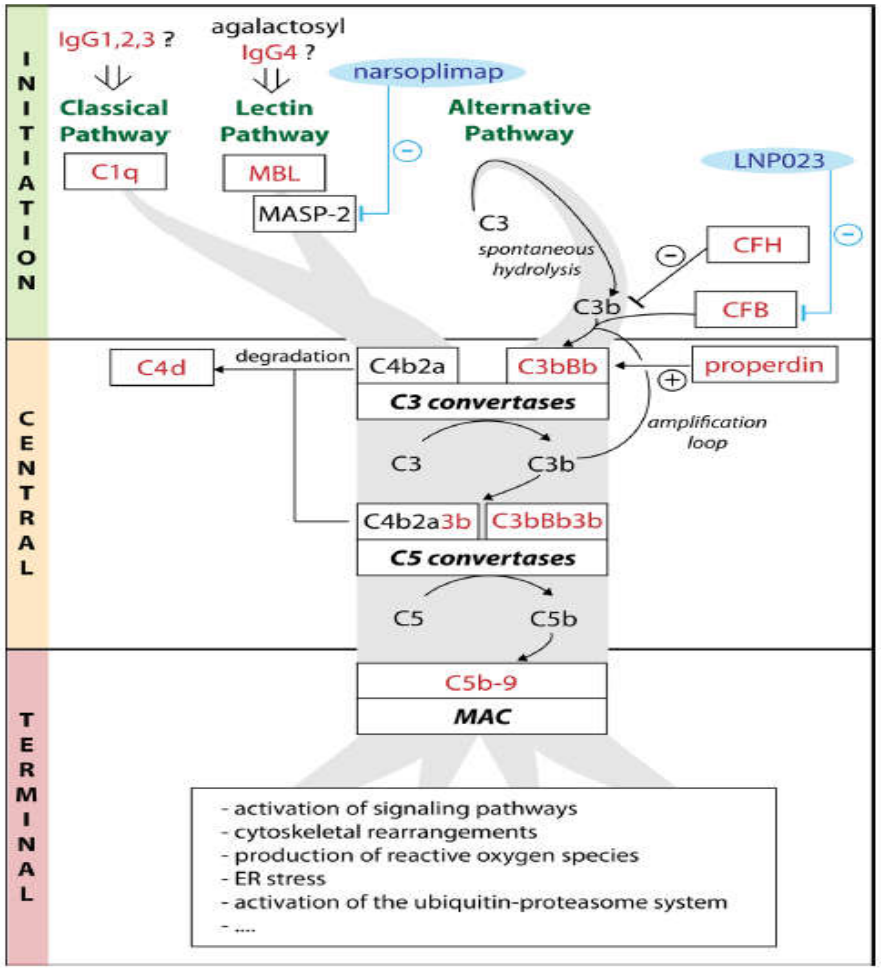
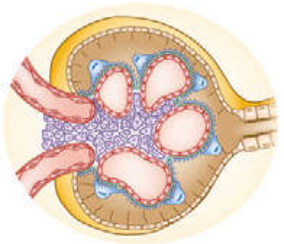


Fig. 2. Schematic overview of the complement cascade in MN.
Components important for the complement cascade in MN are visualized. Components, which are stained by histopathologic techniques in kidney biopsies, are colored in red. Complement inhibitors, which are currently in clinical trials, are highlighted in blue.

Molecular Immunology 128 (2020) 195–204



nature COMMUNICATIONS

ARTICLE

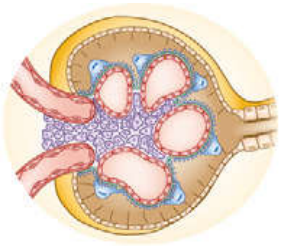
https://doi.org/10.1038/s41467-020-15383-w OPEN

Check for updates

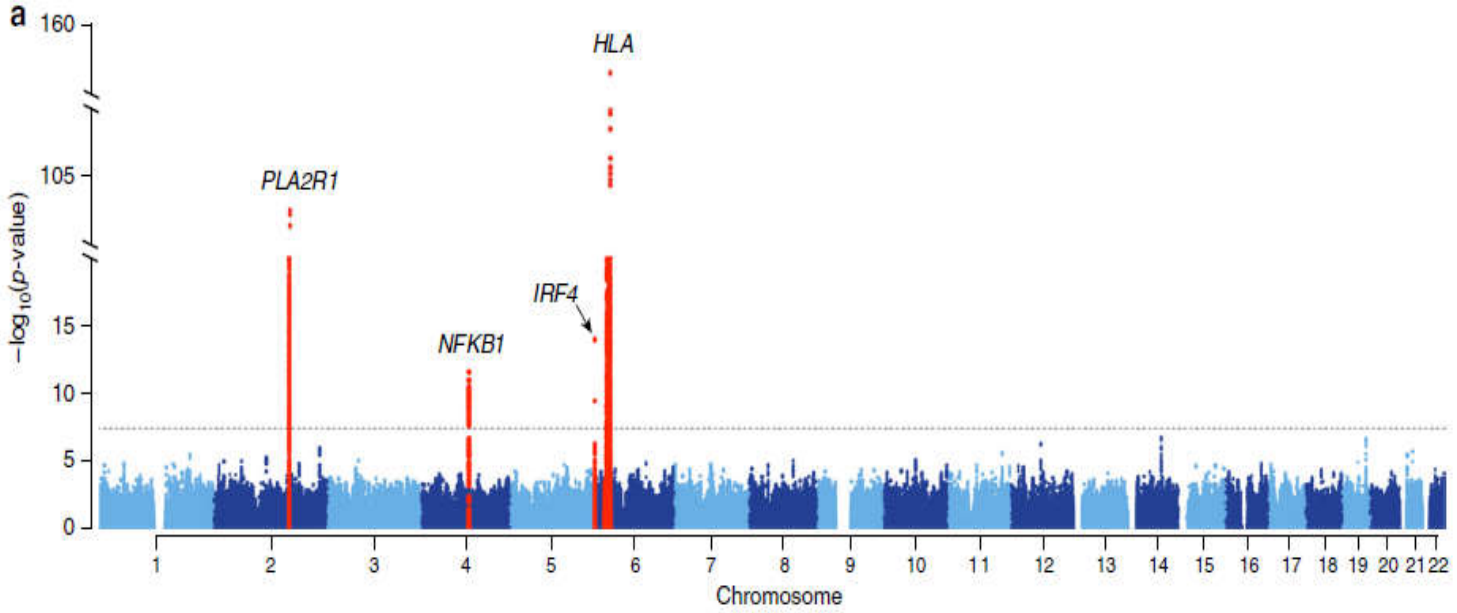
The genetic architecture of membranous nephropathy and its potential to improve non-invasive diagnosis

Jingyuan Xie et al.#

Membranous Nephropathy (MN) is a rare autoimmune cause of kidney failure. Here we report a genome-wide association study (GWAS) for primary MN in 3,782 cases and 9,038 controls of East Asian and European ancestries. We discover two previously unreported loci, *NFKB1* (rs230540, OR = 1.25, $P = 3.4 \times 10^{-12}$) and *IRF4* (rs9405192, OR = 1.29, $P = 1.4 \times 10^{-14}$), fine-map the *PLA2R1* locus (rs17831251, OR = 2.25, $P = 4.7 \times 10^{-103}$) and report ancestry-specific effects of three classical HLA alleles: *DRB1*1501* in East Asians (OR = 3.81, $P = 2.0 \times 10^{-49}$), *DQA1*0501* in Europeans (OR = 2.88, $P = 5.7 \times 10^{-93}$), and *DRB1*0301* in both ethnicities (OR = 3.50, $P = 9.2 \times 10^{-23}$ and OR = 3.39, $P = 5.2 \times 10^{-82}$, respectively). GWAS loci explain 32% of disease risk in East Asians and 25% in Europeans, and correctly re-classify 20–37% of the cases in validation cohorts that are antibody-negative by the serum anti-PLA2R ELISA diagnostic test. Our findings highlight an unusual genetic architecture of MN, with four loci and their interactions accounting for nearly one-third of the disease risk.



HLADR3
HLADQA1
HLADRB1
HLADRB3



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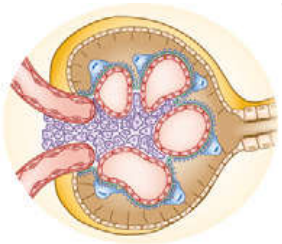

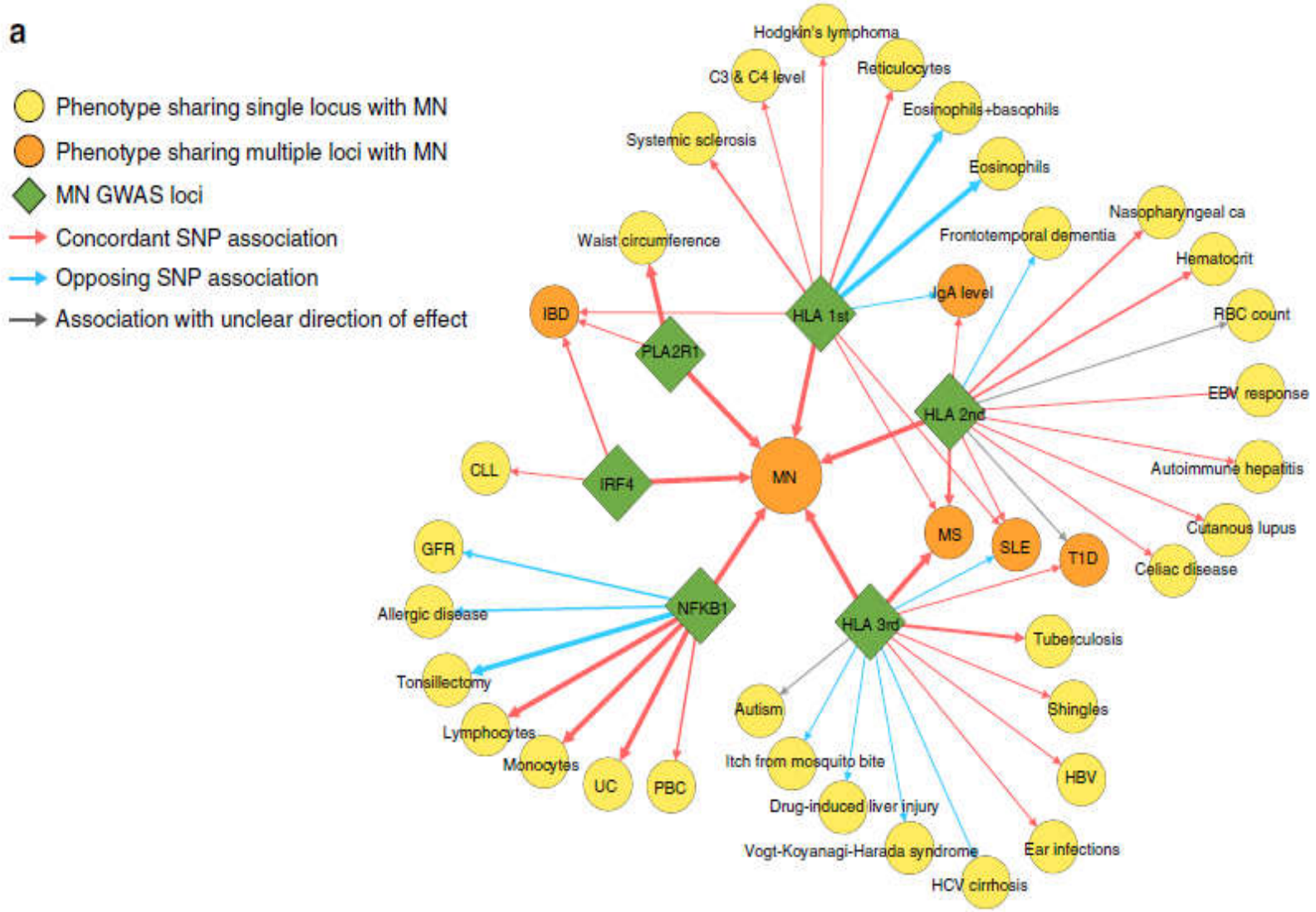

Pleiotropic effects of the MN loci and their clinical correlations

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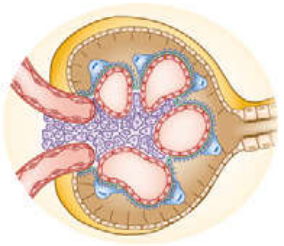


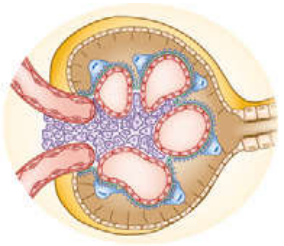
ORIGINAL RESEARCH ARTICLE

WILEY Journal of Cellular Physiology

Upregulated microRNAs in membranous glomerulonephropathy are associated with significant downregulation of IL6 and MYC mRNAs

Cristina Barbagallo[1*] | Roberta Passanisi[1,2*] | Federica Mirabella[1] | Matilde Cirnigliaro[1] | Arianna Costanzo[3] | Giovanni Lauretta[1] | Davide Barbagallo[1] | Cristina Bianchi[4] | Fabio Pagni[5] | Sergio Castorina[2,6] | Antonio Granata[7†] | Cinzia Di Pietro[1†] | Marco Ragusa[1,8†] | Lorenzo S. Malatino[3†] | Michele Purrello[1†]

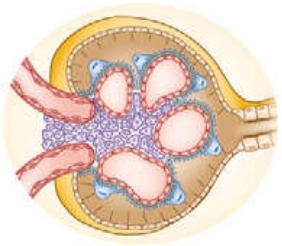
Ten miRNAs (let-7a-5p, let-7b-5p, let-7c-5p, let-7d-5p, miR-107, miR-129-3p, miR-423-5p, miR-516-3p, miR-532-3p, and miR-1275) were differentially expressed (DE) in MGN biopsies compared to unaffected controls



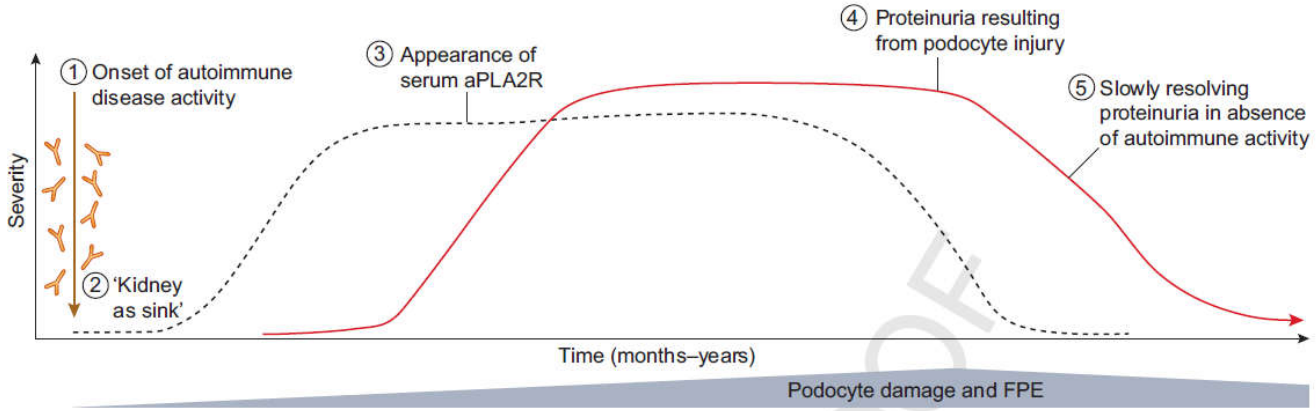
The modern era: serological management of MN

Stages of PMN:

- Immunological initiation phase
- seropositive preclinical phase
- active phase
- immunological recovery phase
- immunological remission (clinical recovery) phase
- clinical remission



Graphical representation of the distinct phases of primary membranous nephropathy



	Phase 1 Immunologic initiation	Phase 2 Seropositive preclinical	Phase 3 Active disease		Phase 4 Immunologic recovery	Phase 5 Immunologic remission
Production of aPLA2R	+	++	+++	++	–	–
Renal deposition of aPLA2R	+	++	+++	++	+	–
Serum aPLA2R	–	+	+++	++	+	–
Proteinuria	–	+/–	++	+	+	+/–

Figure 2| Graphical representation of the distinct phases of primary membranous nephropathy. Changes over time in serum autoantibody levels (dotted line), clinical disease activity (represented by proteinuria; solid line), and podocyte damage and foot process effacement are shown schematically. The serological, immunological, and pathological findings for each phase are shown in the table below the graph. aPLA2R, autoantibody against phospholipase A2 receptor; FPE, XXXX.

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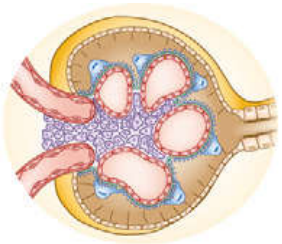

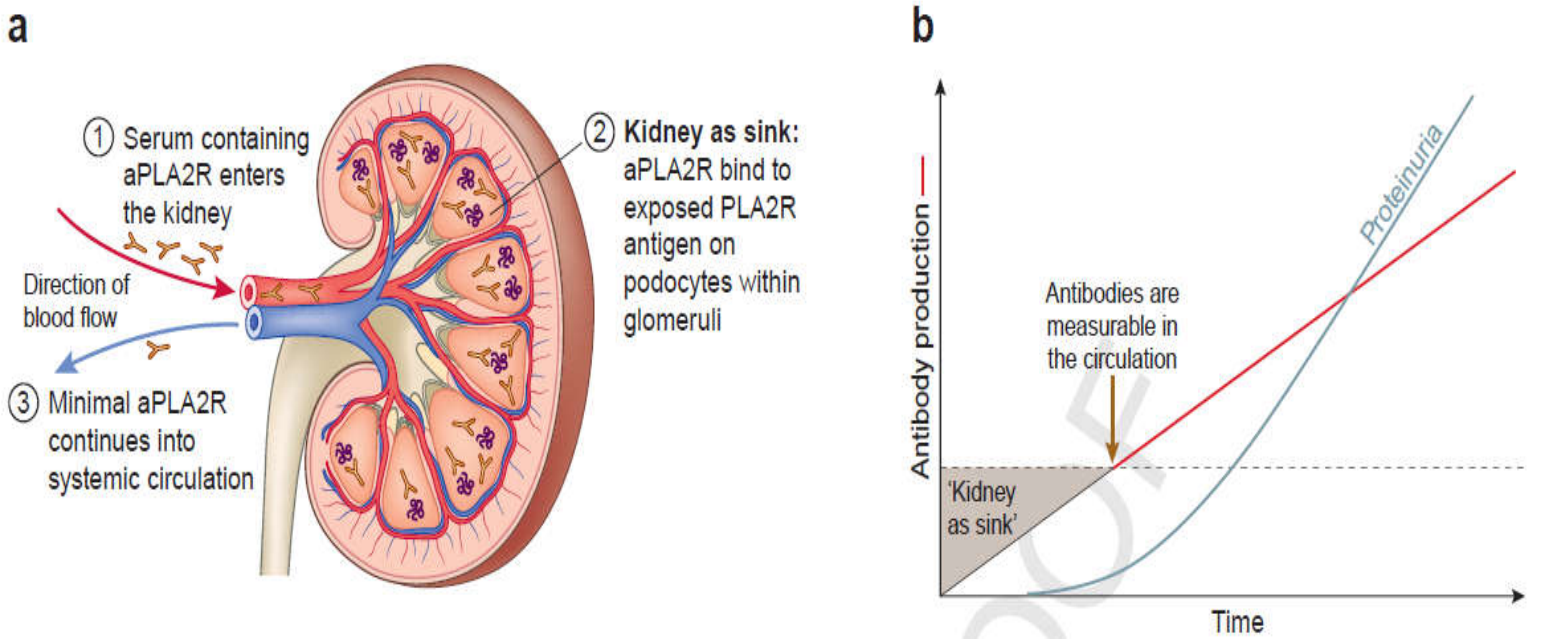

Figure 3 | The "kidney as sink" hypothesis explains the initial absence of circulating autoantibody in primary membranous nephropathy (PMN). (**a**) During early generation of autoantibodies against podocyte antigens in PMN, the relatively abundant podocyte target antigens act as a sponge or "sink" for anti–phospholipase A2 receptor (PLA2R) autoantibodies (aPLA2R). aPLA2R are therefore prevented from entering the systemic circulation. (**b**) Increasing amounts of antibody (red line) over time eventually saturate available PLA2R on the podocyte and detectable amounts appear in the circulation, followed by increasing levels of proteinuria (blue). This model explains why positive PLA2R staining may be present on biopsy without evidence of serum autoantibodies for a period of time early in the disease course.

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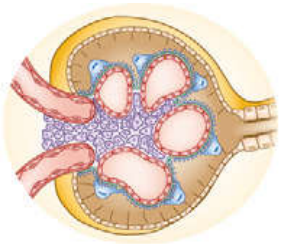
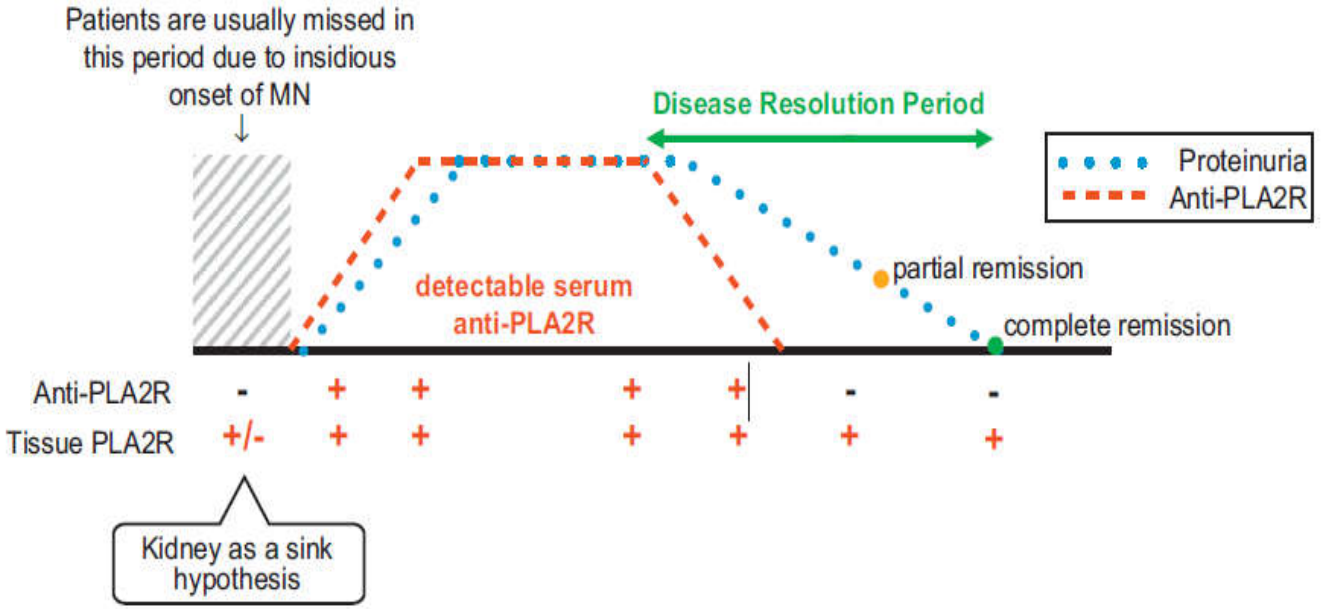
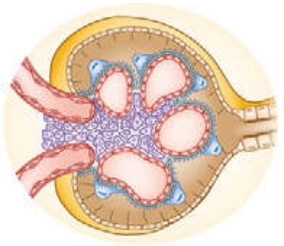




Schematic representation of the immunologic and clinical courses of disease in PLA2R-associated MN.



Clinical recovery and remission

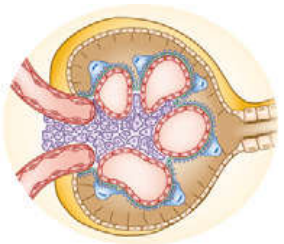
Persistence of proteinuria

significant residual proteinuria that lingers for months to years despite immunological remission.

- longevity of subepithelial deposits (stage 2–3 deposits evolution to stage 4 deposits, 21 months)
- glomerulosclerosis and interstitial fibrosis
- GBM remains abnormal (It may take years before the GBM architecture has normalized)

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

- the sensitivity of a positive PLA2Rab test for the diagnosis of MN was 0.78 and specificity 0.99
- PLA2R antibody testing without kidney biopsy may be a valid strategy to make a non-invasive diagnosis of MN in patients with a negative work-up for secondary causes



Modern Pathology
https://doi.org/10.1038/s41379-019-0267-z

ARTICLE

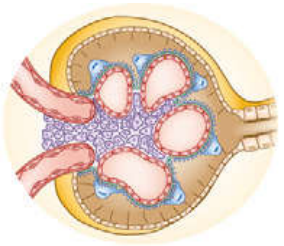
Diagnostic role of renal biopsy in PLA_2R1-antibody-positive patients with nephrotic syndrome

Thorsten Wiech[1] · Rolf A. K. Stahl[2] · Elion Hoxha[2]

Received: 14 January 2019 / Revised: 25 February 2019 / Accepted: 25 February 2019

Abstract

Renal biopsy is the gold standard for diagnosis of membranous nephropathy. Circulating PLA_2R1 antibody found in 75% of patients with membranous nephropathy is very specific for the diagnosis of this disease. Therefore, the question arises whether PLA_2R1-antibody-positive patients still need a diagnostic renal biopsy. In this study we investigated whether additional relevant information is obtained by performing renal biopsy in nephrotic patients, who are PLA_2R1-antibody positive. A detailed analysis of renal biopsies, including immunohistochemistry and electron microscopy, was performed in 263 patients with biopsy-proven membranous nephropathy, of whom 194 patients were PLA_2R1-antibody positive, to detect diagnostic features additional to membranous nephropathy. Twelve (6%) of the 194 PLA_2R1-antibody-positive patients had a second relevant diagnosis in addition to membranous nephropathy: five (3%) patients had interstitial nephritis, in five (3%) other patients a diabetic nephropathy was diagnosed and two (1%) patients had IgA nephropathy. Patients with a second diagnosis in addition to membranous nephropathy had a significantly higher serum creatinine ($p < 0.01$) and lower eGFR ($p = 0.04$) compared to patients in whom only the diagnosis of membranous nephropathy was made. In 7 (10%) of 69 PLA_2R1-antibody-negative patients, renal biopsies showed an additional diagnosis to membranous nephropathy: one (1%) case of IgA nephropathy, cholesterol emboli, IgG4-related disease, necrotising glomerulonephritis, thrombotic microangiopathy, interstitial nephritis and diabetic nephropathy each. The advantage of detecting an additional diagnosis to membranous nephropathy in 6% of PLA_2R1-antibody-positive patients by renal biopsy has to be balanced to the potential risks and costs of the biopsy procedure. Renal biopsy is particularly relevant in patients presenting with impaired renal function and abnormalities in urinalysis going beyond proteinuria. Immunohistochemical staining for PLA_2R1 was the only histomorphologic analysis allowing a reliable differentiation of PLA_2R1-antibody-positive from PLA_2R1-antibody-negative membranous nephropathy.



www.kidney-international.org clinical investigation

Noninvasive diagnosis of primary membranous nephropathy using phospholipase A2 receptor antibodies

see commentary on page 265

OPEN

Shane A. Bobart[1,4], An S. De Vriese[2,4], Aditya S. Pawar[1], Ladan Zand[1], Sanjeev Sethi[3], Callen Giesen[3], John C. Lieske[1,3] and Fernando C. Fervenza[1]

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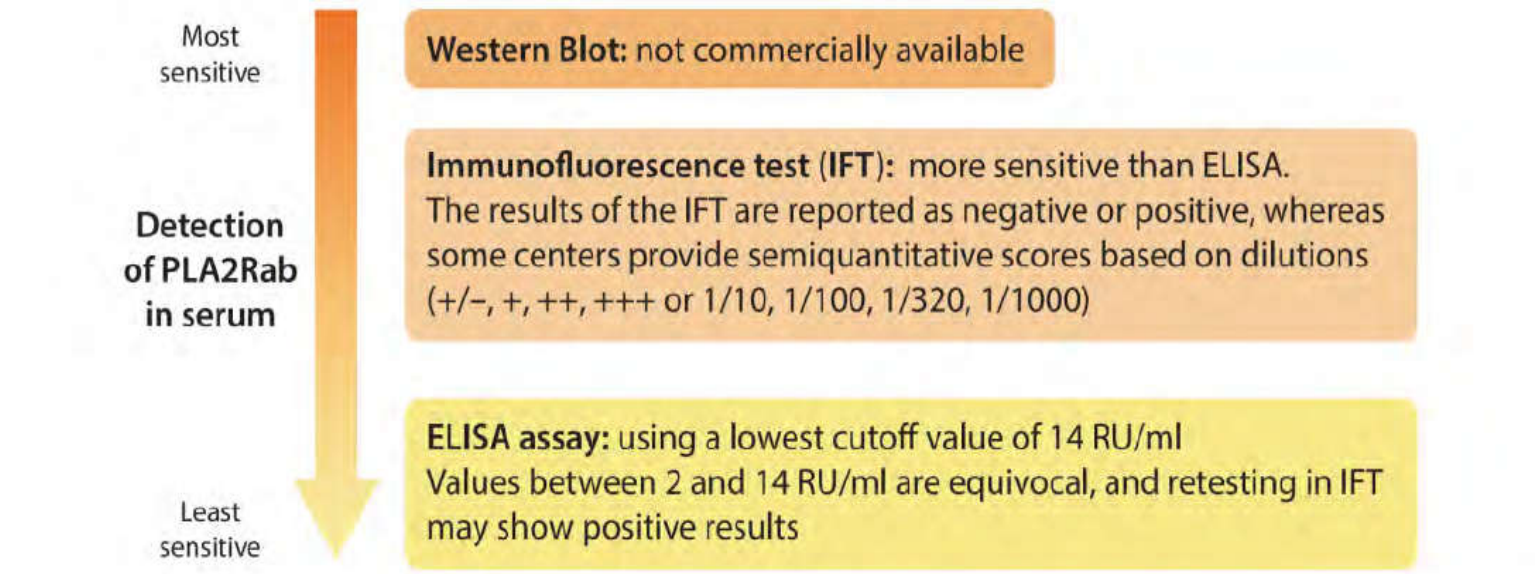
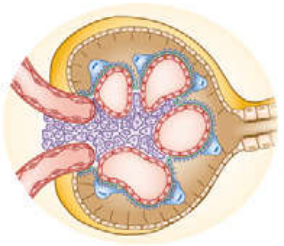
Ninety-seve patients had a negative work-up for secondary causes o MN. Sixty of those 97 patients had an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73m2. In these patients, the kidney biopsy did not provide significant information that altered management; one patient had a superimposed diabetic nephropathy and a second patient had a superimposed focal segmental glomerulosclerosis (FSGS) lesion.

Conclusion: Among patients with preserved kidney function and no evidence of secondary causes, a positive PLA2R antibody test highly predicts a tissue diagnosis of PLA2R-associated MN

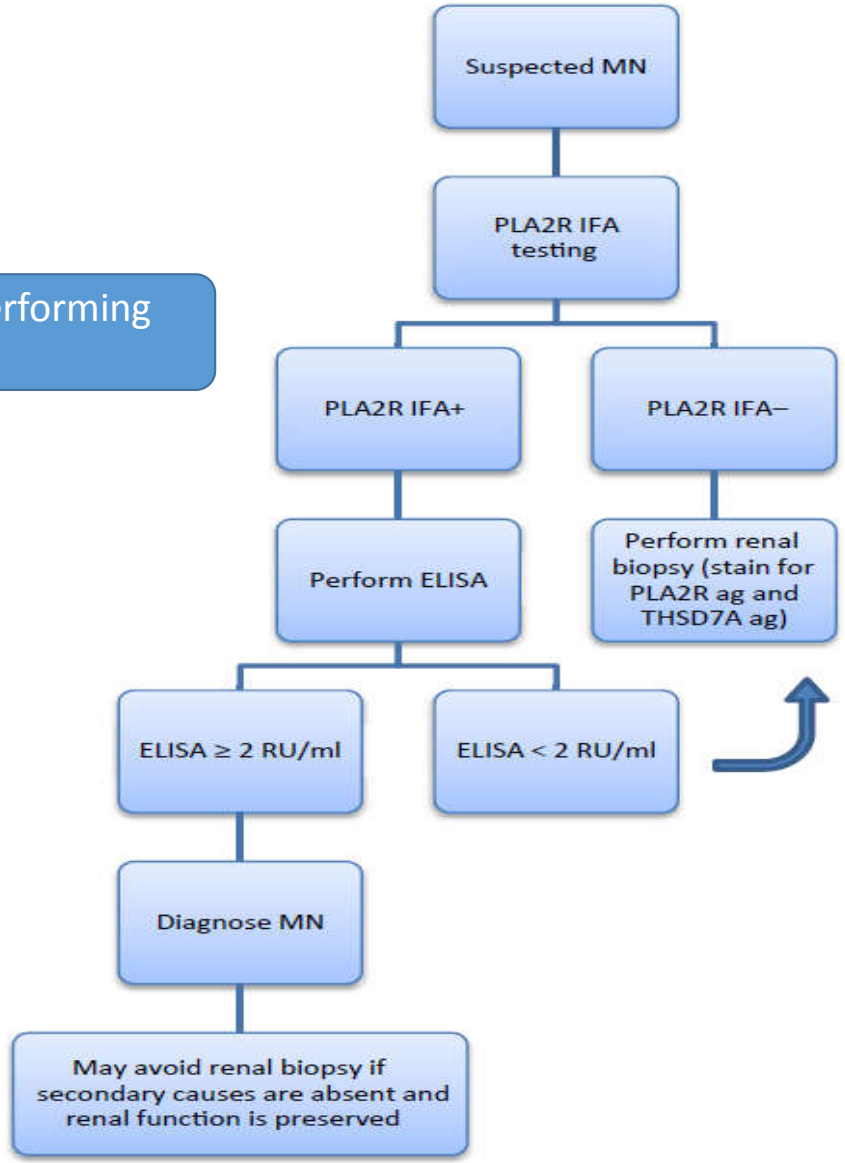
Kidney International (2019) 95, 429–438

Guidance for the use and interpretation of the PLA2Rab assay in patients with known PLA2R-associated MN





Algorithm for centers preferentially performing immunofluorescence assays (IFAs).



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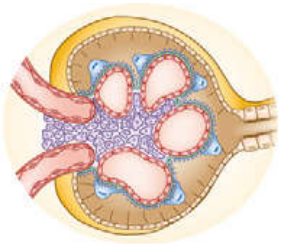
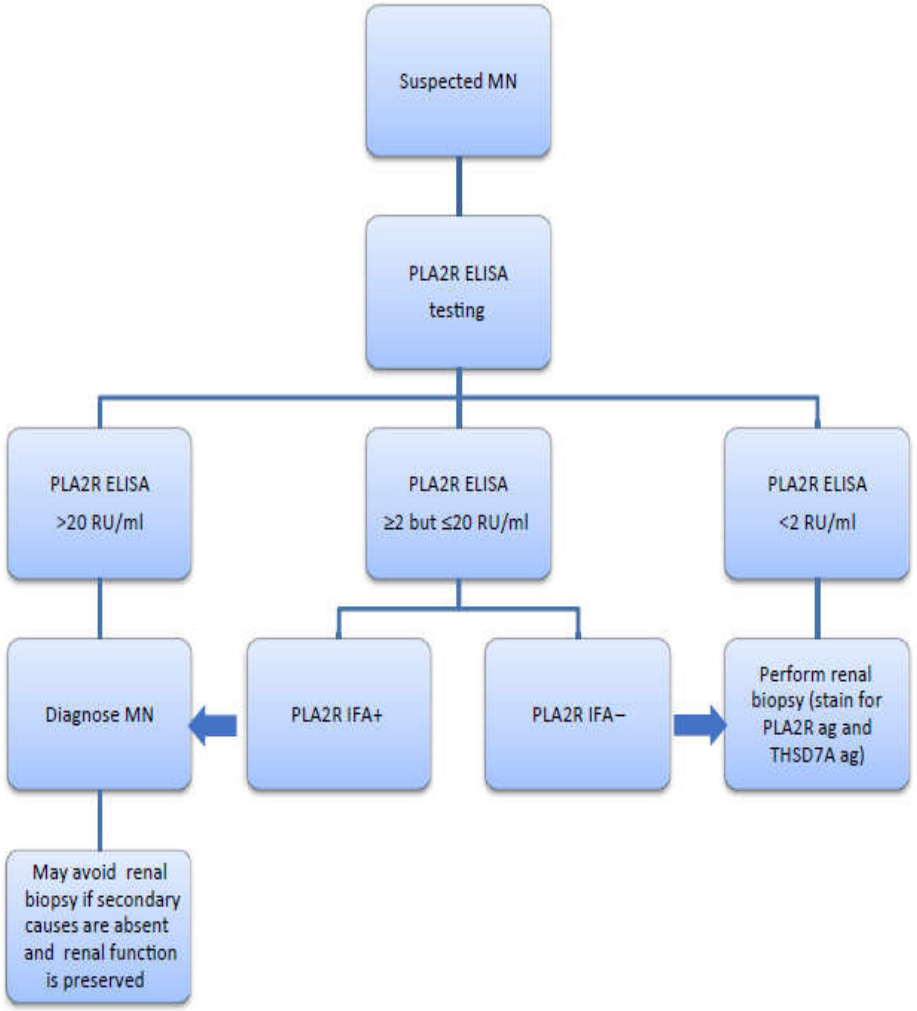
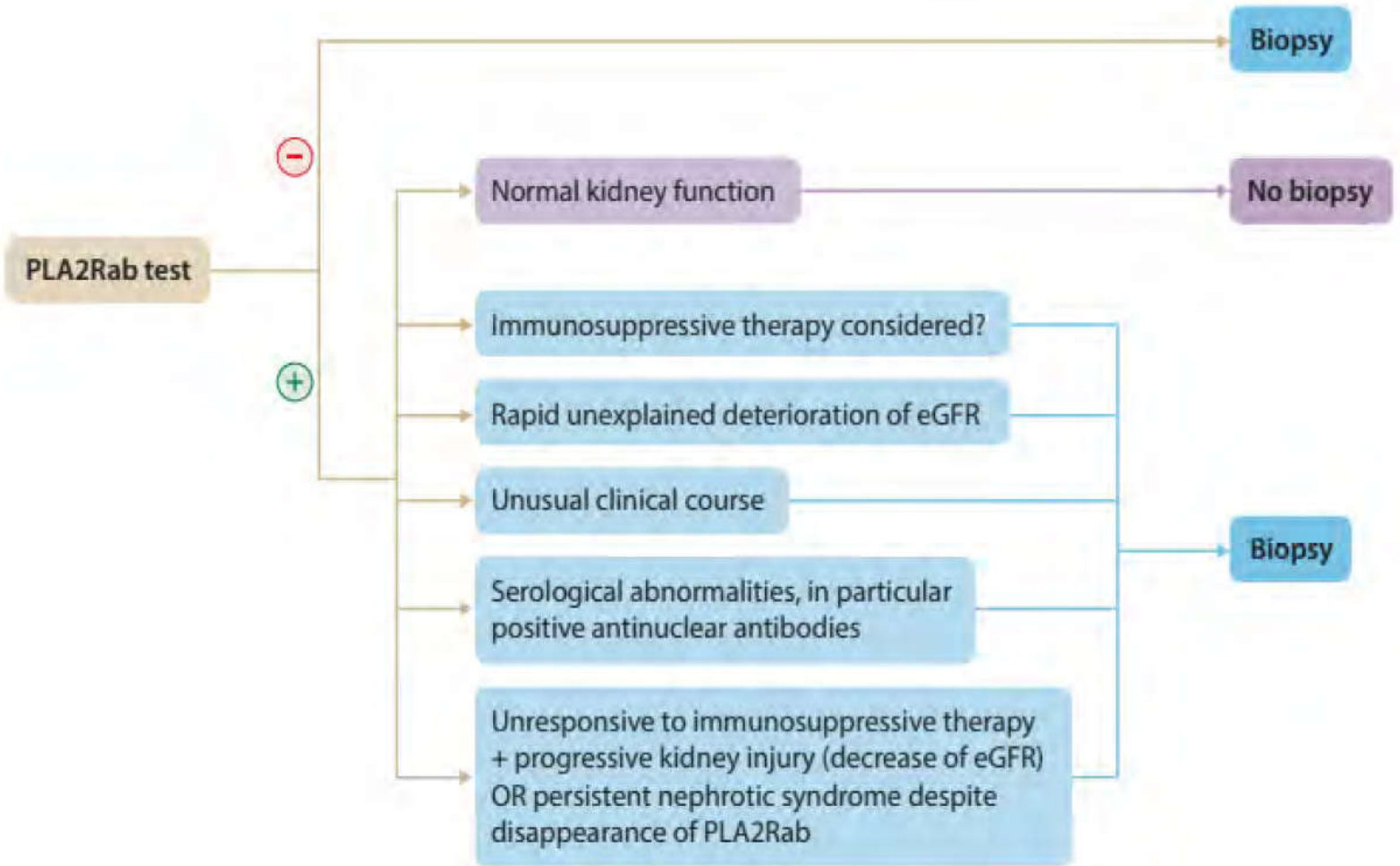


Algorithm for centers preferentially performing enzyme-linked immunosorbent assays (ELISAs).

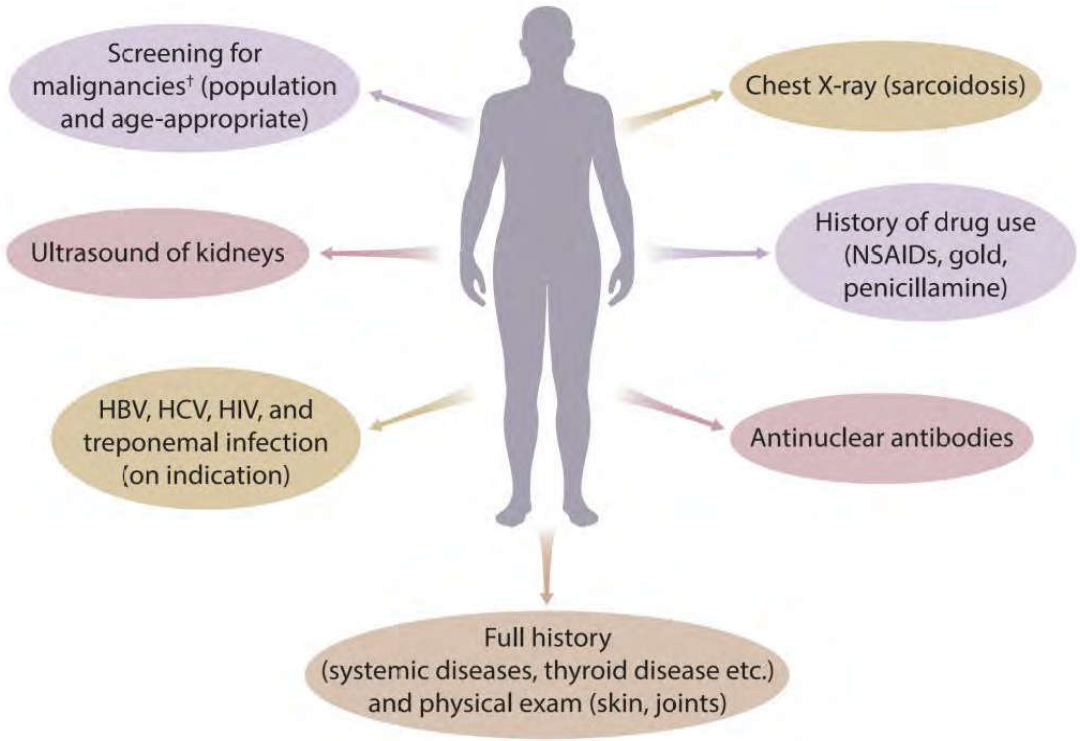


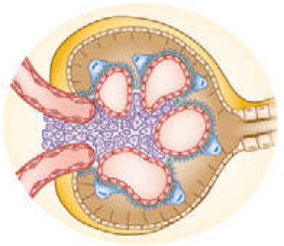
Kidney International (2019) 95, 429–438

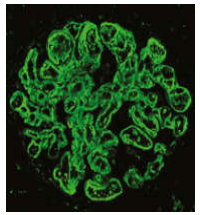
When to consider a kidney biopsy in a PLA2Rab-positive patient



Patients with MN should be evaluated for associated conditions, regardless of whether PLA2Rab and/or TSHD7Aab are present or absent

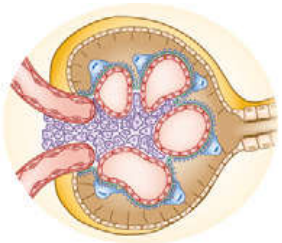






Risk factors for progression	Good prognosis
Age	Complete remission of proteinuria
Male sex	Partial remission of proteinuria
Decreased GFR on presentation	Long duration of remission
Increased excretion of some LMW markers such as β2 microglobulin	
Persistent elevated anti-PLA2R or THSD7A levels after therapy	Low anti-PLA2R or THSD7A levels or decreased levels
Anti-PLA2R against CTLD1, CTLD7 domain*	Anti-PLA2R against CysR domain
C3 staining in the biopsy sample	
Increased urinary excretion of C3dg and C5b-9	
Risk alleles*: HLA-DQR1; PLA2R1 HLA-DRB	

*Presence of risk alleles for both HLA and PLA2R raises the risk for PMN up to 79-fold



Phospholipase A2 Receptor 1 Epitope Spreading at Baseline Predicts Reduced Likelihood of Remission of Membranous Nephropathy

BRIEF COMMUNICATION

Barbara Seitz-Polski,[1,2,3] Hanna Debiec,[4,5] Alexandra Rousseau,[6] Karine Dahan,[7] Christelle Zaghrini,[1] Christine Payré,[1] Vincent LM. Esnault,[3] Gérard Lambeau,[1] and Pierre Ronco[4,5,7]

[1]Institut de Pharmacologie Moléculaire et Cellulaire, Centre National de la Recherche Scientifique, Université Côte d'Azur, Sophia Antipolis, Valbonne, France; [2]Laboratoire d'Immunologie and [3]Service de Néphrologie, Centre Hospitalier Universitaire de Nice, Université Côte d'Azur, Nice, France; [4]Université Pierre et Marie Curie, Sorbonne Universités, Paris, France; [5]Unité Mixte de Recherche 1155, Institut National de la Santé et de la Recherche Médicale, Paris, France; [6]Unité de Recherche Clinique de l'Est Parisien, hôpital Saint-Antoine, Assistance Publique Hôpitaux de Paris, Paris, France; and [7]Department of Nephrology and Dialysis, hôpital Tenon, Assistance Publique Hôpitaux de Paris, Paris, France

ABSTRACT

The phospholipase A2 receptor (PLA2R1) is the major autoantigen in primary membranous nephropathy. Several PLA2R1 epitopes have been characterized, and a retrospective study identified PLA2R1 epitope spreading as a potential indicator of poor prognosis. Here, we analyzed the predictive value of anti-PLA2R1 antibody (PLA2R1-Ab) titers and epitope spreading in a prospective cohort of 58 patients positive for PLA2R1-Ab randomly allocated to rituximab (n=29) or antiproteinuric therapy alone (n=29). At baseline, the epitope profile (CysR, CysRC1, CysRC7, or CysRC1C7) did not correlate with age, sex, time from diagnosis, proteinuria, or serum albumin, but epitope spreading strongly correlated with PLA2R1-Ab titer (P<0.001). Ten (58.8%) of the 17 patients who had epitope spreading at baseline and were treated with rituximab showed reversal of epitope spreading at month 6. In adjusted analysis, epitope spreading at baseline was associated with a decreased remission rate at month 6 (odds ratio, 0.16; 95% confidence interval, 0.04 to 0.72; P=0.02) and last follow-up (median, 23 months; odds ratio, 0.14; 95% confidence interval, 0.03 to 0.64; P=0.01), independently from age, sex, baseline PLA2R1-Ab level, and treatment group. We propose that epitope spreading at baseline be considered in the decision for early therapeutic intervention in patients with primary membranous nephropathy.

J Am Soc Nephrol 29: 401–408, 2018. doi: https://doi.org/10.1681/ASN.2017070734

outcome.[6,7] Therefore, reducing PLA2R1-Ab level has become an important goal of therapy. Although the identification of PLA2R1-Ab has been paradigm shifting in the diagnosis and management of patients, there are cases that call for additional biomarkers. Indeed, antibodies may persist during apparent clinical remission, and conversely, a drop in antibody titer may not be associated with a clinical remission.[7,8]

PLA2R1 is a 180-kDa membrane receptor with a large extracellular region

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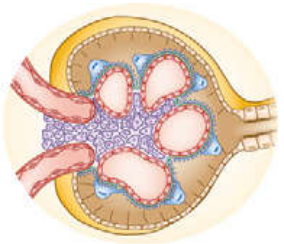
B.S.-P., H.D., and A.R. contributed equally to this work.

G.L. and P.R. contributed equally to this work.



Traditional approach to a patient with MN-related proteinuria

J. Clin. Med. **2021**, 10, 1205

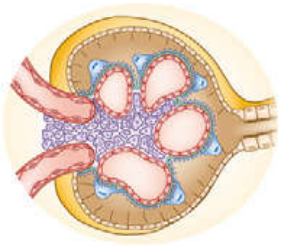
In patients with MN, use clinical and laboratory criteria to assess the risk of progressive loss of kidney function

Because spontaneous remission is relatively common in MN and because immunosuppressive treatment has adverse effects, it is important to assess the risk of progressive loss of kidney function prior to deciding about whether and when to implement immunosuppressive treatment

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

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.



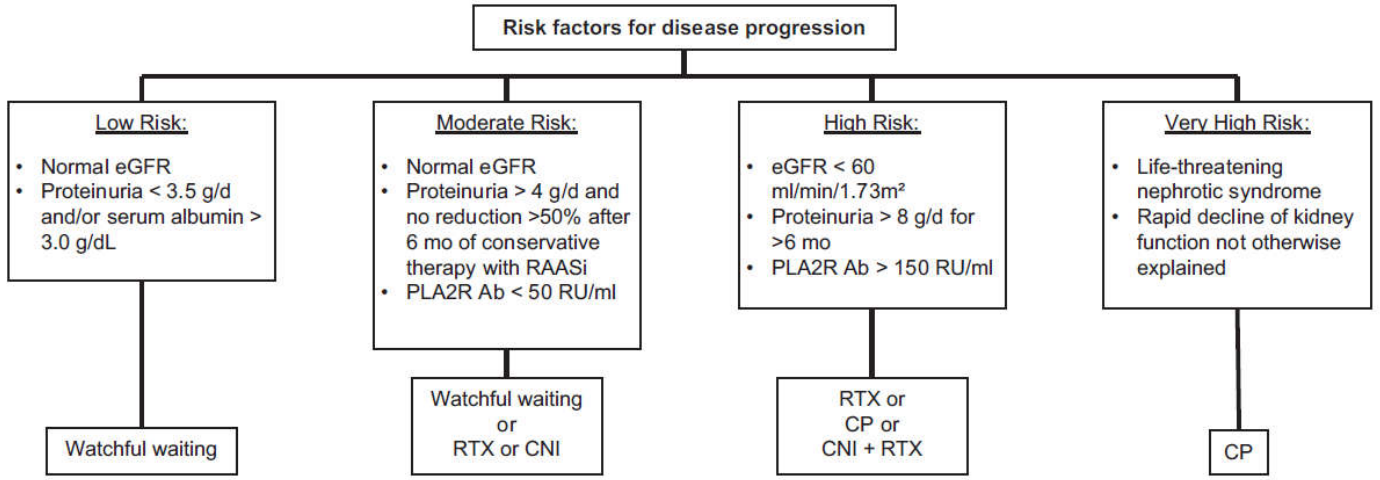


Figure 5. This algorithm classifies patients into 4 different risk groups with the subsequent recommended therapy plan. The thresholds for anti-PLA_2R titer are somewhat arbitrary. Consideration should also be given to anti-PLA_2R trajectory, as a decreasing titer over time might warrant continued monitoring with antiproteinuric therapy alone, whereas increasing titer might increase the level of risk. Abbreviations: CP, cyclophosphamide-based protocol; eGFR, estimated glomerular filtration rate; Ab, antibody; RAASi, renin-angiotensin-aldosterone system inhibition; RTX, rituximab.

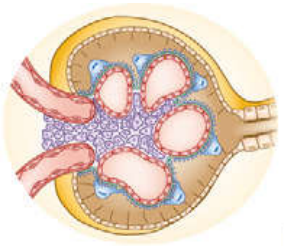
Considerations for treatment of patients with primary MN:

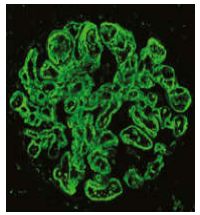
- All patients with primary MN and proteinuria should receive optimal supportive care.
- Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury

Commonly used treatment regimens for patients with MN

Cyclophosphamide (cyclical)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d in months 1, 3, and 5 • Cyclophosphamide 2.5 mg/kg/d in months 2, 4, and 6‡
Cyclophosphamide (continuous)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d every other day in months 1–6, with taper thereafter • Cyclophosphamide 1.5 mg/kg/d in months 1–6‡
Rituximab	• Rituximab 1 g i.v. administered twice within 2 weeks* • Rituximab 375 mg/m^2 given 1–4 times at weekly intervals
Tacrolimus	• Tacrolimus 0.05–0.1 mg/kg/d, target trough level 3–8 µg/ml, duration 12 months†
Cyclosporine	• Cyclosporine 3.5 mg/kg/d, target trough level 125–225 µg/ml†

Cyclosporine and tacrolimus are often given in combination with prednisone in a dose of 10 mg/day. After four months, withdrawal if no response; after 12 months, consider tapering to lower levels.





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

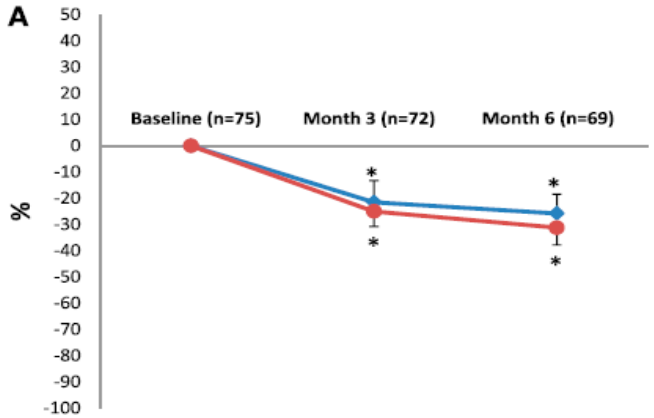
Karine Dahan,* Hanna Debiec,[†‡] Emmanuelle Plaisier,*[†‡] Marine Cachanado,[§] Alexandra Rousseau,[§] Laura Wakselman,[§] Pierre-Antoine Michel,* Fabrice Mihout,* Bertrand Dussol,[‖] Marie Matignon,[¶] Christiane Mousson,** Tabassome Simon,[§] and Pierre Ronco,*[†‡] on behalf of the GEMRITUX Study Group

*Department of Nephrology and Dialysis, Assistance Publique Hôpitaux de Paris, Hôpital Tenon, Paris, France; [†]Sorbonne Universités, Université Pierre et Marie Curie Paris 06, Paris, France; [‡]Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche 1155, Paris, France; [§]Department of Clinical Pharmacology and Unité de Recherche Clinique, Assistance Publique Hôpitaux de Paris, Hôpital Saint Antoine, Paris, France; [‖]Department of Nephrology and Transplantation, Assistance Publique-Hôpitaux de Marseille, Hôpital de la Timone, Marseille, France; [¶]Department of Nephrology and Transplantation, Assistance Publique Hôpitaux de Paris, Hôpital Henri Mondor, Creteil, France; and **Department of Nephrology and Transplantation, Centre Hospitalier Universitaire, Dijon, France

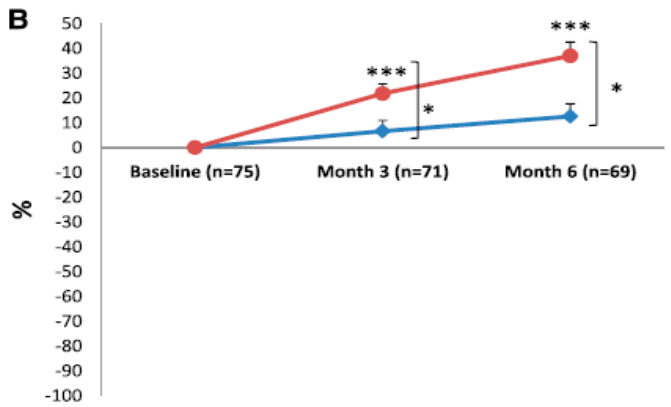
Positive effect of rituximab on proteinuria remission occurred after 6 months. These data suggest that PLA2R-Ab levels are early markers of rituximab effect and that addition of rituximab to NIAT does not affect safety.

J Am Soc Nephrol 28: 348–358, 2017

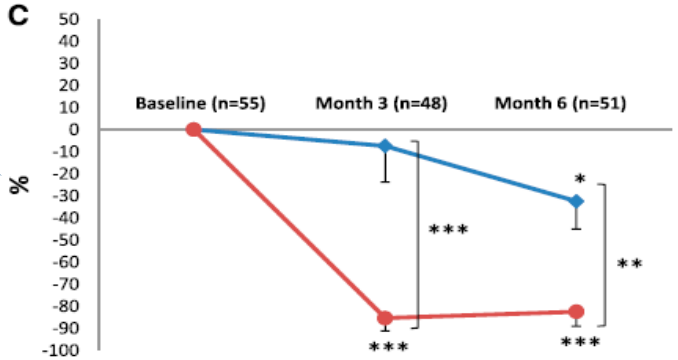
proteinuria



serum albumin

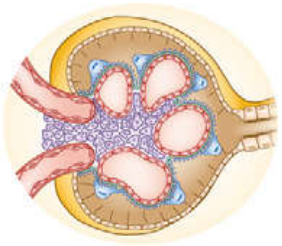


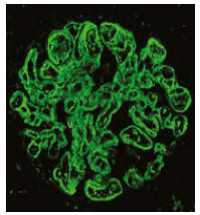
anti–PLA2R-Ab levels



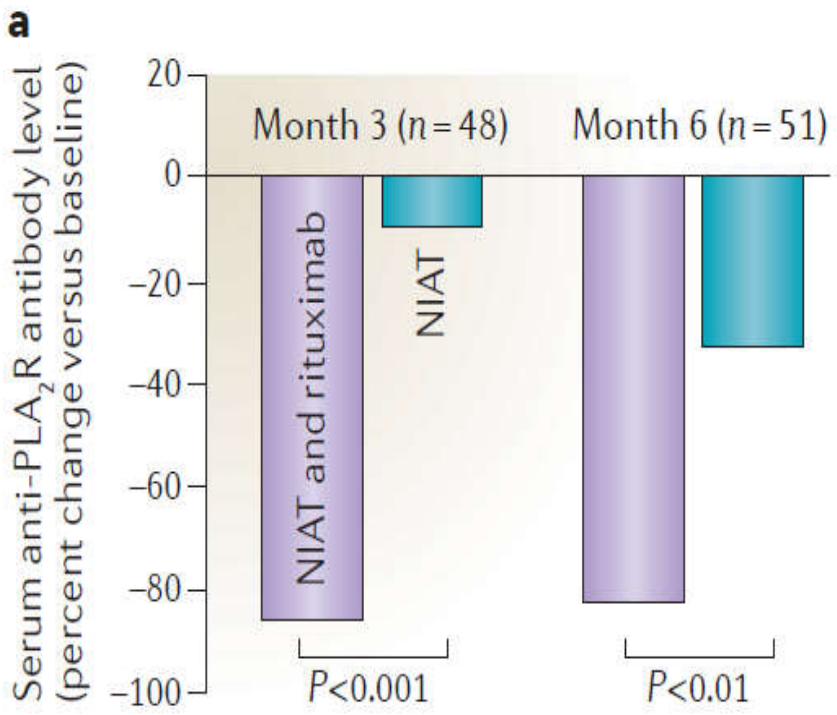
NIAT

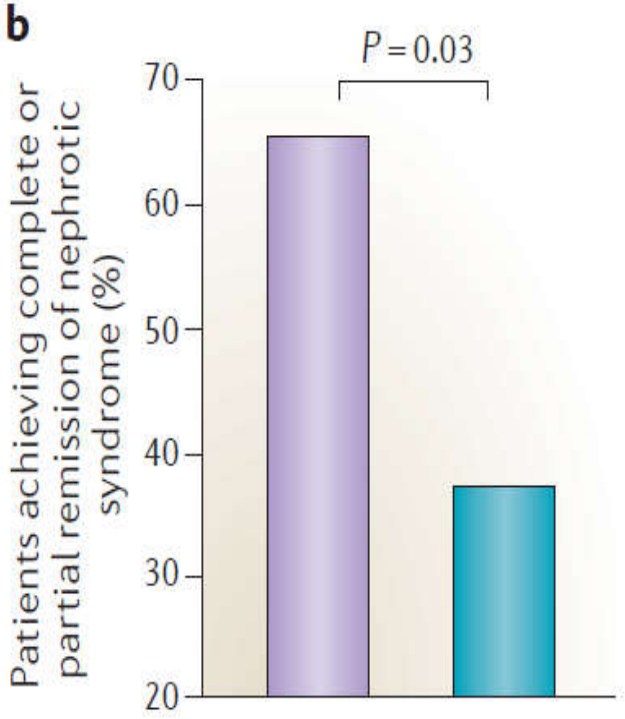
NIAT-rituximab



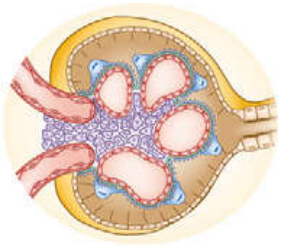


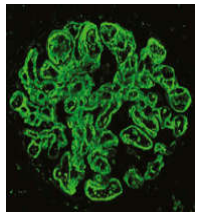
Key findings from the GEMRITUX trial





Nature review, nephrology, 13(563-579), September 2017





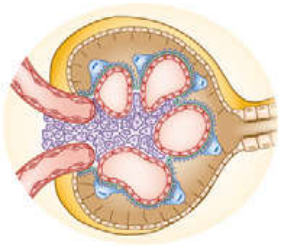
Safety of Rituximab Compared with Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy

Jan A.J.G. van den Brand,* Piero Ruggenenti,†‡ Antonietta Chianca,‡ Julia M. Hofstra,* Annalisa Perna,‡ Barbara Ruggiero,‡ Jack F.M. Wetzels,* and Giuseppe Remuzzi†‡

*Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands; †Unit of Nephrology, Azienda Socio Sanitaria Territoriale Ospedale Papa Giovanni XXIII, Bergamo, Italy; and ‡IRCCS - Instituto di Ricerche Farmacologiche "Mario Negri", Department of Renal Medicine, Clinical Research Center for Rare Diseases "Ado e Cele Daccò", Ranica, Bergamo, Italy

Rituximab (RTX) may be a safer alternative, lower partial remission rates with rituximab versus cyclophosphamide, rates of complete remission and the composite renal end point did not differ significantly between groups

J Am Soc Nephrol 28: 2729–2737, 2017



Pharmacology

Original Paper

Pharmacology 2013;91:259–266
DOI: 10.1159/000348570

Received: December 5, 2012
Accepted after revision: January 23, 2013
Published online: May 7, 2013

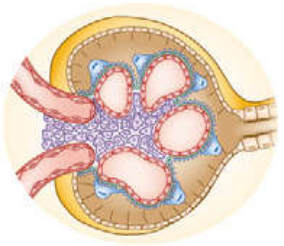
Effect of Prolonged Tacrolimus Treatment in Idiopathic Membranous Nephropathy with Nephrotic Syndrome

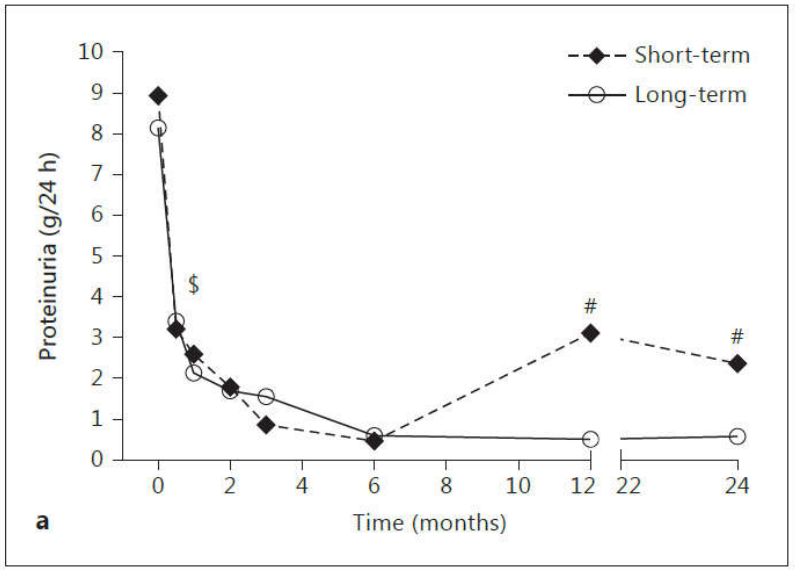
Hang Yuan[a] Nian Liu[b] Guang-Dong Sun[a] Ye Jia[a] Ping Luo[a] Li-Ning Miao[a]

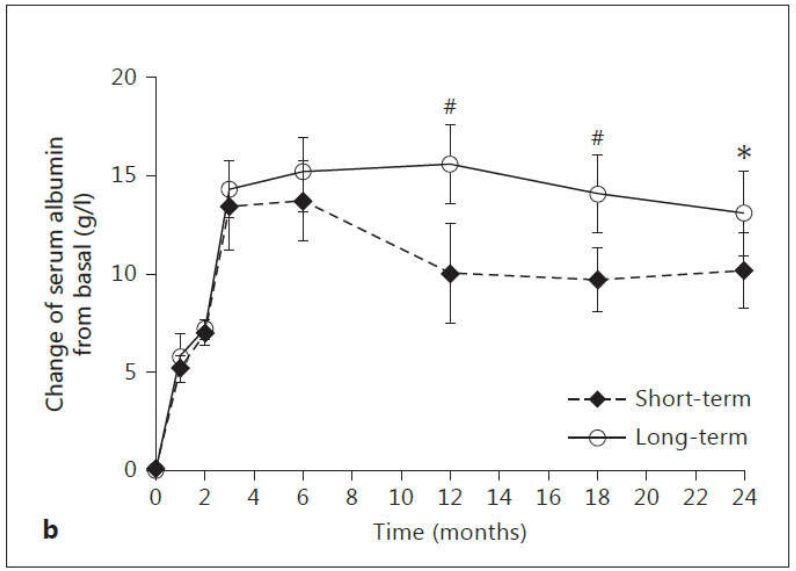
Departments of [a]Nephrology and [b]Tumor Biotherapy, Second Hospital of Jilin University, Changchun, China

Results: Over 85% of the patients achieved proteinuria reduction, serum albumin improvement and serum lipid recovery; the probability of remission in both groups was over 80% at 6 months. The remission rate was steady at over 80% after 12 and 24 months in the long-term group, but only 50 and 45%, respectively, in the short-term group. Nine patients (45%) relapsed in the short-term group after tacrolimus withdrawal, while not a single patient suffered recurrence in the long-term group

Conclusion: Combined therapy of tacrolimus with prednisone can relieve IMN significantly; prolonged tacrolimus treatment at a low blood concentration can alleviate the illness persistently, with a low recurrence rate and gratifying safety.

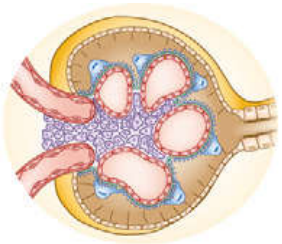






Average of 24-hour urinary protein excretion levels (g/24 h) and change in serum albumin (mean ± SD g/l) from the baseline value at each follow-up evaluation in the short-term (n = 20) and long-term treated patients (n = 22) during the study period

Pharmacology 2013;91:259–266



Journal of the Formosan Medical Association (2016) 115, 11–18

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

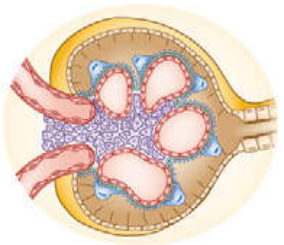
Comparison of different therapies in high-risk patients with idiopathic membranous nephropathy

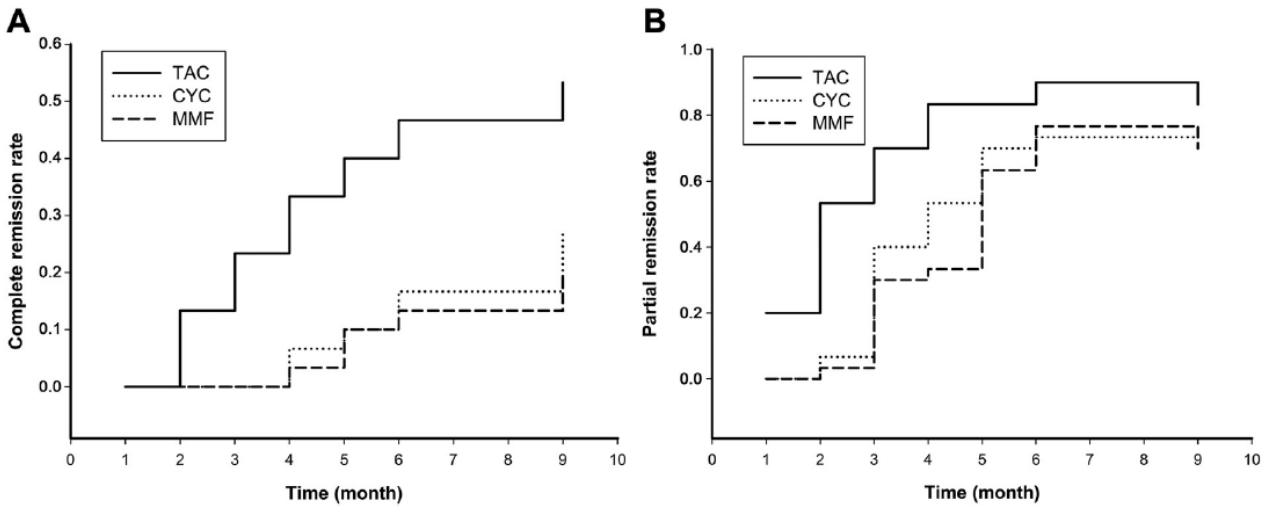
Lei Peng [a], Shi-Yao Wei [a], Lei-Ting Li, Yi-Xin He, Bing Li*

Department of Nephrology, 2nd Affiliated Hospital, Harbin Medical University, Harbin, People's Republic of China

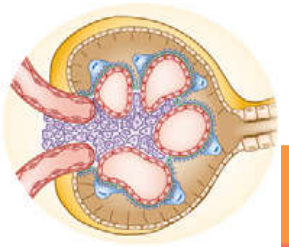
Received 17 April 2015; received in revised form 19 July 2015; accepted 27 July 2015

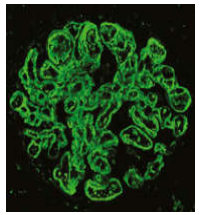
Conclusion: Tacrolimus combined with corticosteroid had tolerable adverse effects and induced the remission of IMN more effectively and more rapidly. This is the first prospective randomized cohort study to compare three different therapies in patients at high risk for IMN. It provides strong evidence for choosing optimal treatment for patients with IMN.





Probability of complete remission and partial remission in the tacrolimus, cyclophosphamide, and cyclophosphamide groups.





NEPHROLOGY

APSN

Nephrology **21** (2016) 139–146

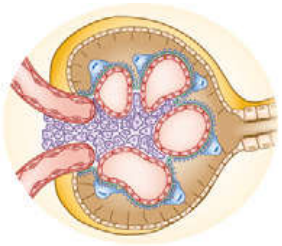
Original Article

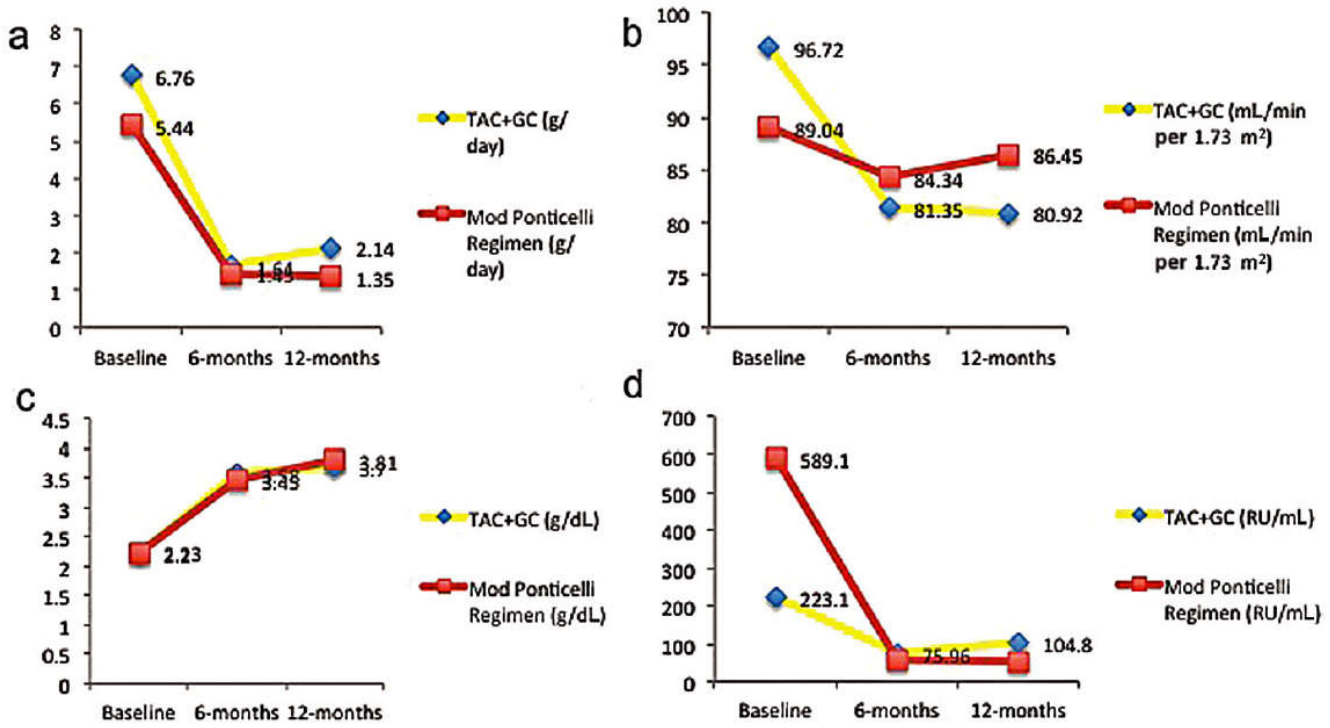
Tacrolimus combined with corticosteroids versus Modified Ponticelli regimen in treatment of idiopathic membranous nephropathy: Randomized control trial

RAJA RAMACHANDRAN,[1] HARSHA KUMAR HN,[1] VINOD KUMAR,[1] RITAMBHRA NADA,[2] ASHOK KUMAR YADAV,[1] AJAY GOYAL,[1] VIVEK KUMAR,[1] MANISH RATHI,[1] VIVEKANAND JHA,[1] KRISHAN LAL GUPTA,[1] VINAY SAKHUJA[1] and HARBIR SINGH KOHLI[1]

Departments of [1]Nephrology and [2]Histopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Both TAC and MPR are comparable in induction remission, but with different adverse effect profile and with higher relapse rate

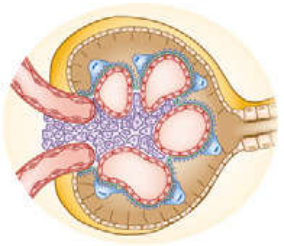




(a) Urine protein in both the groups at baseline, 6 and 12 months. (b) Estimated glomerular filtration rate (eGFR) in both the groups at baseline, 6 and 12 months. (c) Serum albumin in both the groups at baseline, 6 and 12 months. (d) PLA2R antibodies in both the groups at baseline, 6 and 12 months.*

There was a significant reduction in eGFR in patients receiving TAC* ($P = 0.009$).

Nephrology **21** (2016) 139–146



KI REPORTS
KIReports.org
CLINICAL RESEARCH

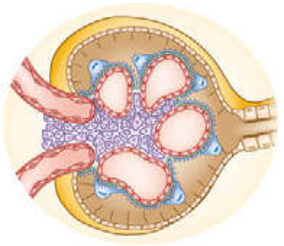
Two-Year Follow-up Study of Membranous Nephropathy Treated With Tacrolimus and Corticosteroids Versus Cyclical Corticosteroids and Cyclophosphamide

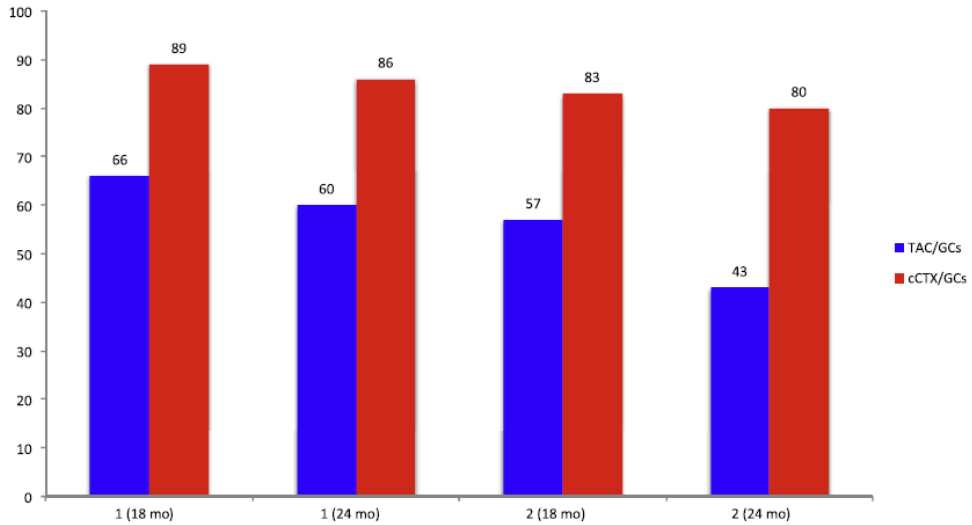
Raja Ramachandran[1], Ashok Kumar Yadav[1], Vinod Kumar[1], Venkata Siva Tez Pinnamaneni[1], Ritambhra Nada[2], Ratan Ghosh[1], Vivek Kumar[1], Manish Rathi[1], Harbir Singh Kohli[1], Krishan Lal Gupta[1], Vinay Sakhuja[1] and Vivekanand Jha[3,4]

[1]Department of Nephrology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [2]Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [3]Department of Nephrology, Oxford University, Oxford, UK; and [4]The George Institute for Global Health, New Delhi, India

At 2 years after randomization, relapse rates are higher for TAC/GCs compared with cCTX/GCs in PMN patients. Thus, cCTX/GCs are better than TAC/GCs in the longer term in PMN patients.

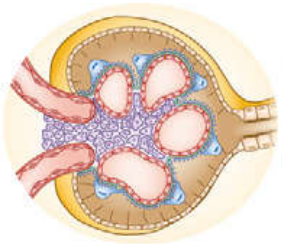
Kidney International Reports (2017) 2, 610–616





Remission rate at various time points

Kidney International Reports (2017) 2, 610–616



J Korean Med Sci. 2018 Feb 26;33(9):e74
https://doi.org/10.3346/jkms.2018.33.e74
eISSN 1598-6357·pISSN 1011-8934

JKMS

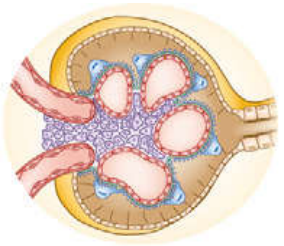
Original Article
Nephrology

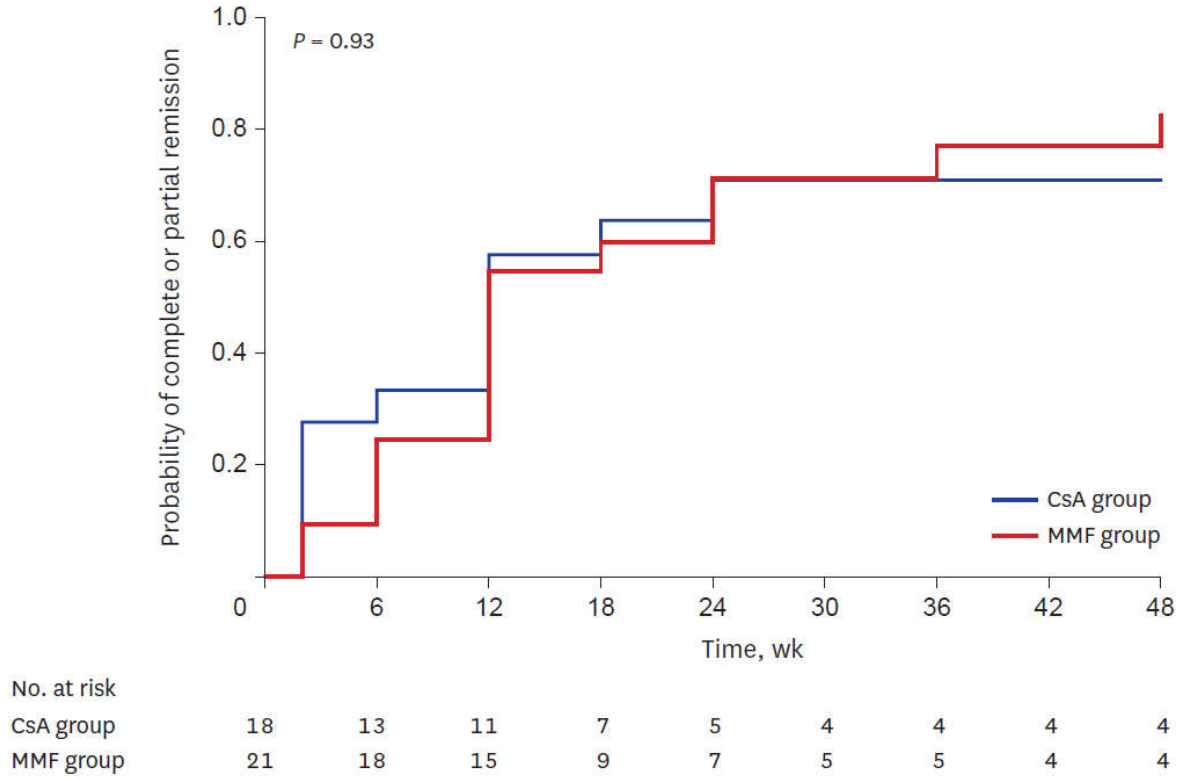
Check for updates

OPEN ACCESS

The Effect of Mycophenolate Mofetil versus Cyclosporine as Combination Therapy with Low Dose Corticosteroids in High-risk Patients with Idiopathic Membranous Nephropathy: a Multicenter Randomized Trial

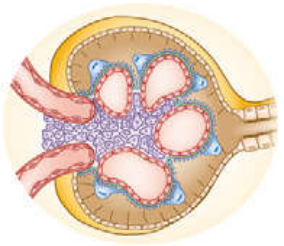
Conclusion: In combination with low-dose corticosteroids, the effect of MMF may not be inferior to that of CsA in patients with idiopathic MN, with similar adverse effects including gastrointestinal symptoms

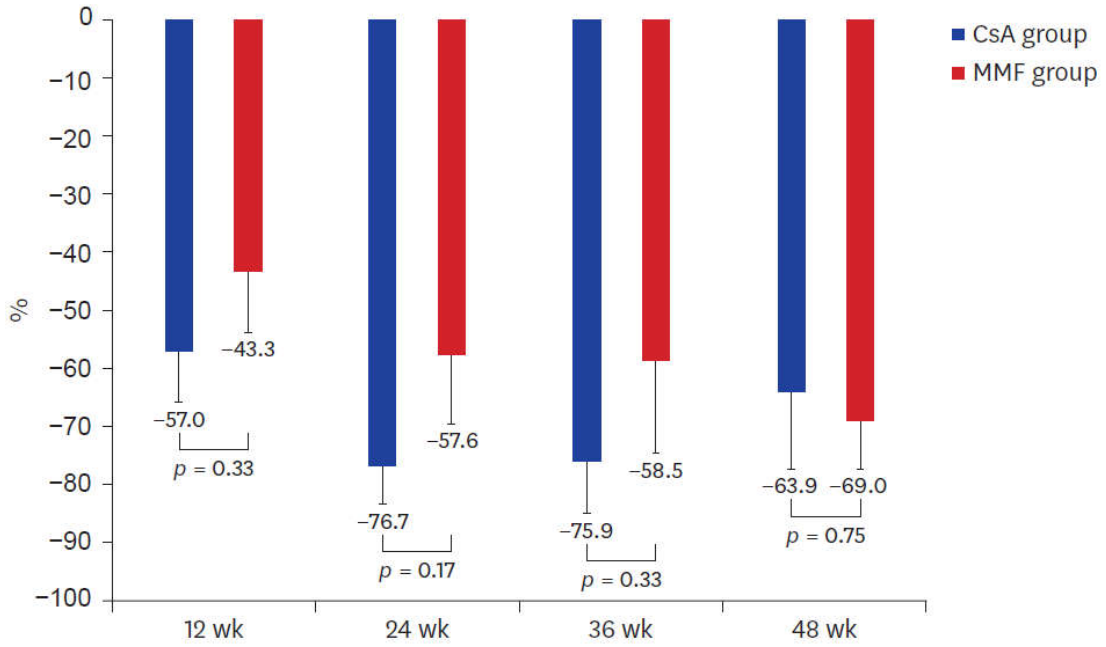




No. at risk									
CsA group	18	13	11	7	5	4	4	4	4
MMF group	21	18	15	9	7	5	5	4	4

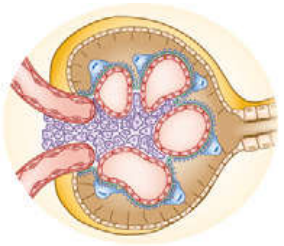
Probability of complete or partial remission of proteinuria in MMF and CsA groups. The cumulative incidence of complete or partial remission of proteinuria at 48 weeks was 82.8% in the MMF group and 70.9% in the CsA group, which did not significantly differ between the groups (*P* = 0.93).

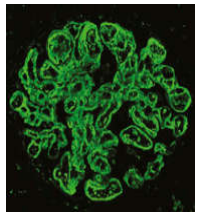




Changes in proteinuria from baseline in MMF and CsA groups. Changes in proteinuria from baseline to 12, 24, 36, and 48 weeks were comparable between the two

J Korean Med Sci. 2018 Feb 26;33(9):e74





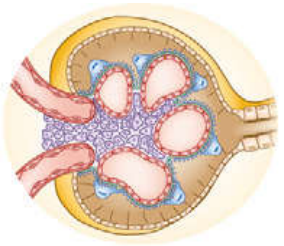
ORIGINAL ARTICLE

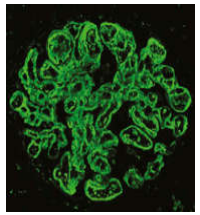
Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy

F.C. Fervenza, G.B. Appel, S.J. Barbour, B.H. Rovin, R.A. Lafayette, N. Aslam, J.A. Jefferson, P.E. Gipson, D.V. Rizk, J.R. Sedor, J.F. Simon, E.T. McCarthy, P. Brenchley, S. Sethi, C. Avila-Casado, H. Beanlands, J.C. Lieske, D. Philibert, T. Li, L.F. Thomas, D.F. Green, L.A. Juncos, L. Beara-Lasic, S.S. Blumenthal, A.N. Sussman, S.B. Erickson, M. Hladunewich, P.A. Canetta, L.A. Hebert, N. Leung, J. Radhakrishnan, H.N. Reich, S.V. Parikh, D.S. Gipson, D.K. Lee, B.R. da Costa, P. Jüni, and D.C. Cattran, for the MENTOR Investigators

Rituximab was non inferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months and was superior in maintaining proteinuria remission up to 24 months.

n engl j med 381;1 nejm.org July 4, 2019





Evaluation Time Point	Rituximab (N=65)	Cyclosporine (N=65)	Risk Difference (95% CI)	P Value for Noninferiority	P Value for Superiority
	no. with complete or partial remission (%)		*percentage points*		
End of treatment period at 12 mo	39 (60)	34 (52)	8 (−9 to 25)	0.004	—
End of follow-up at 24 mo	39 (60)	13 (20)	40 (25 to 55)	<0.001	<0.001

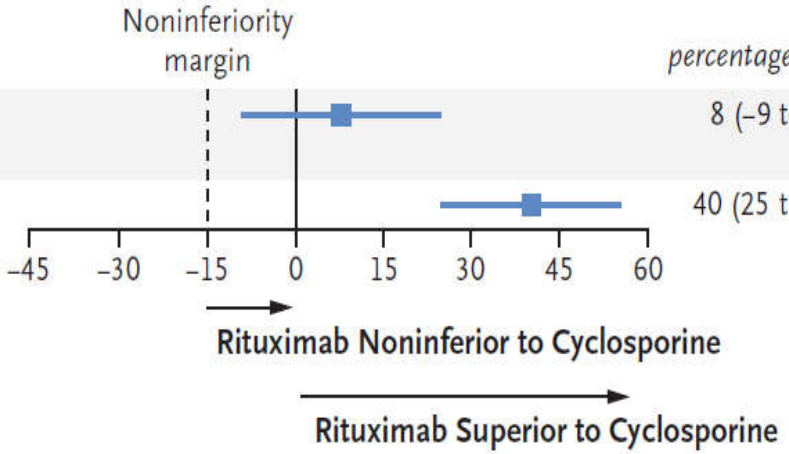
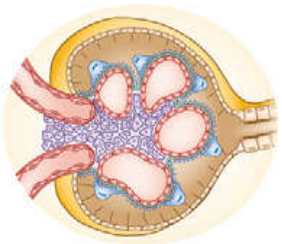


Figure 1. Composite Outcome of Complete or Partial Remission at 12 and 24 Months.

Among patients in remission who tested positive for anti–phospholipase A2 receptor (PLA2R) antibodies, the decline in autoantibodies to anti-PLA2R was faster and of greater magnitude and duration in the rituximab group than in the cyclosporine group



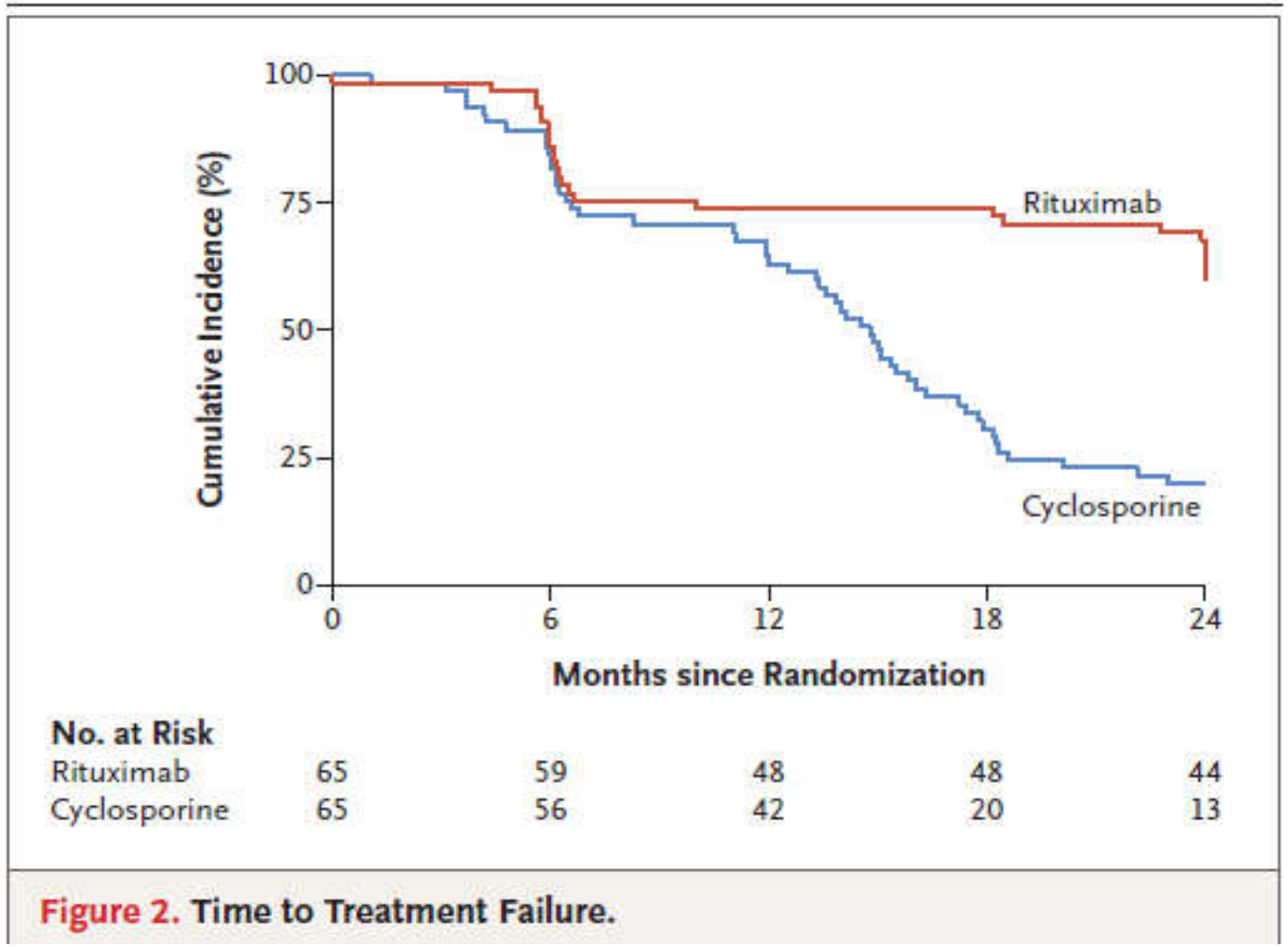
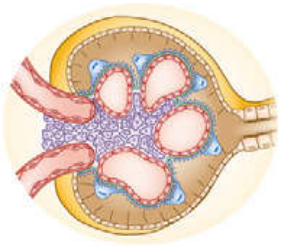


Figure 2. Time to Treatment Failure.



clinical trial www.kidney-international.org

The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy

see commentary on page 811

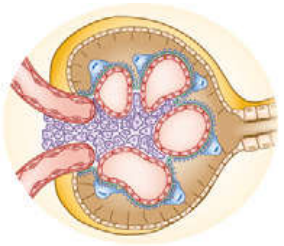
OPEN

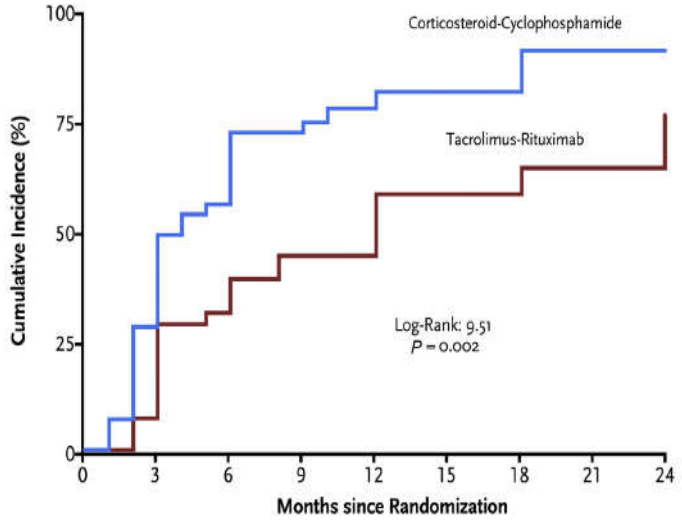
Gema Fernández-Juárez[1], Jorge Rojas-Rivera[2], Anne-Els van de Logt[3], Joana Justino[4], Angel Sevillano[5],

This was tested in a randomized, open-label controlled trial of 86 patients with primary membranous nephropathy and persistent nephrotic syndrome after six-months observation and assigned 43 each to receive six-month cyclical treatment with corticosteroid and cyclophosphamide or sequential treatment with tacrolimus (full-dose for six months and tapering for another three months) and rituximab (one gram at month six).

Conclusion: treatment with corticosteroid cyclophosphamide induced remission in a significantly greater number of patients with primary membranous nephropathy than tacrolimus-rituximab.

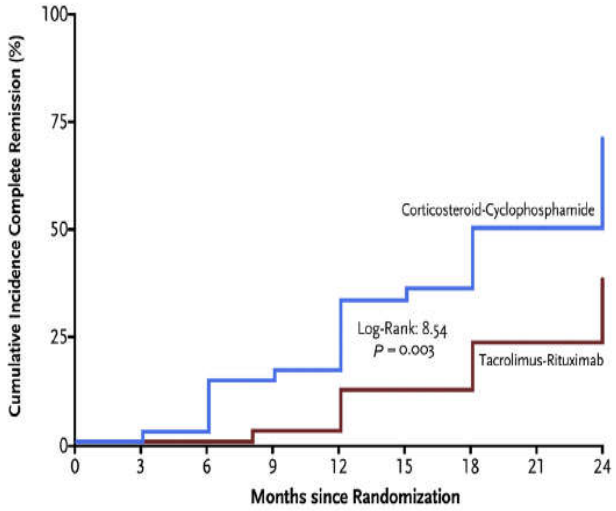
Kidney International (2021) 99, 986–998





No. at Risk									
Corticosteroid-Cyclophosphamide	43	31	19	12	6	4	4	1	1
Tacrolimus-Rituximab	43	39	27	20	16	7	7	6	6

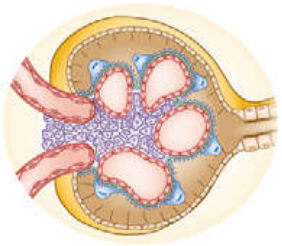
b

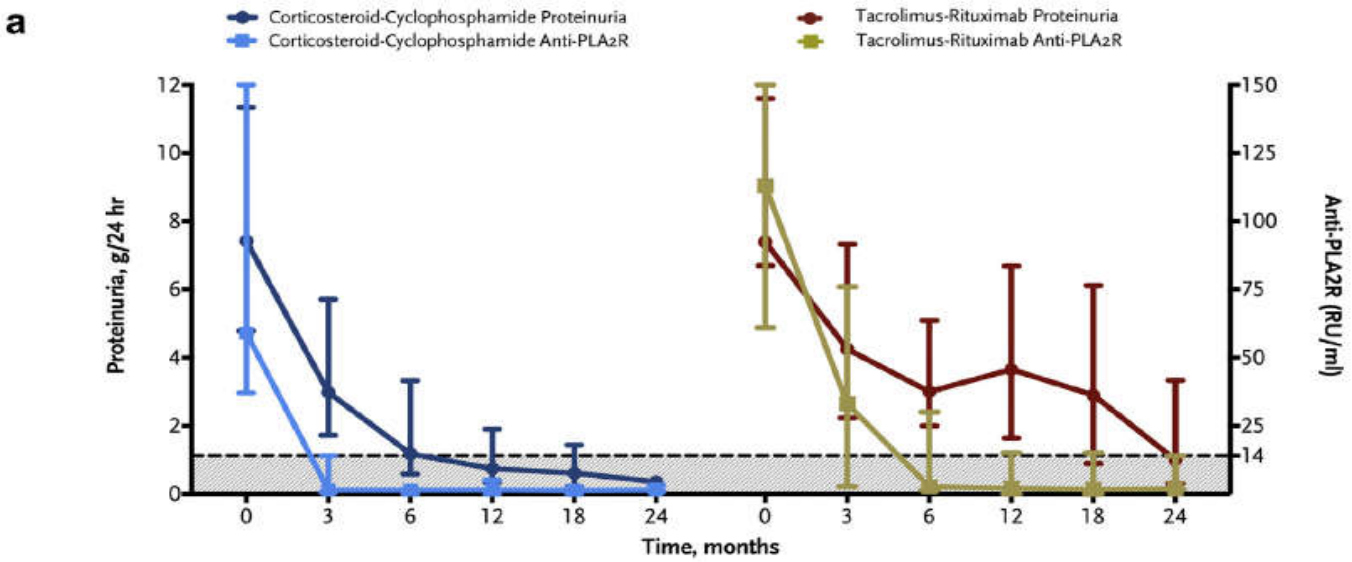


No. at Risk									
Corticosteroid-Cyclophosphamide	43	43	42	37	31	24	23	17	17
Tacrolimus-Rituximab	43	42	40	36	32	24	24	21	21

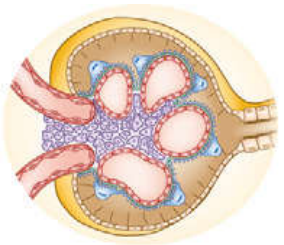
Figure 2| Kaplan-Meier analysis of complete or partial remission. Kaplan-Meier estimates of (**a**) remission (complete or partial) and (**b**) complete remission in the corticosteroid-cyclophosphamide and tacrolimus-rituximab groups.

Kidney International (2021) 99, 986–998





Kidney International (2021) 99, 986–998



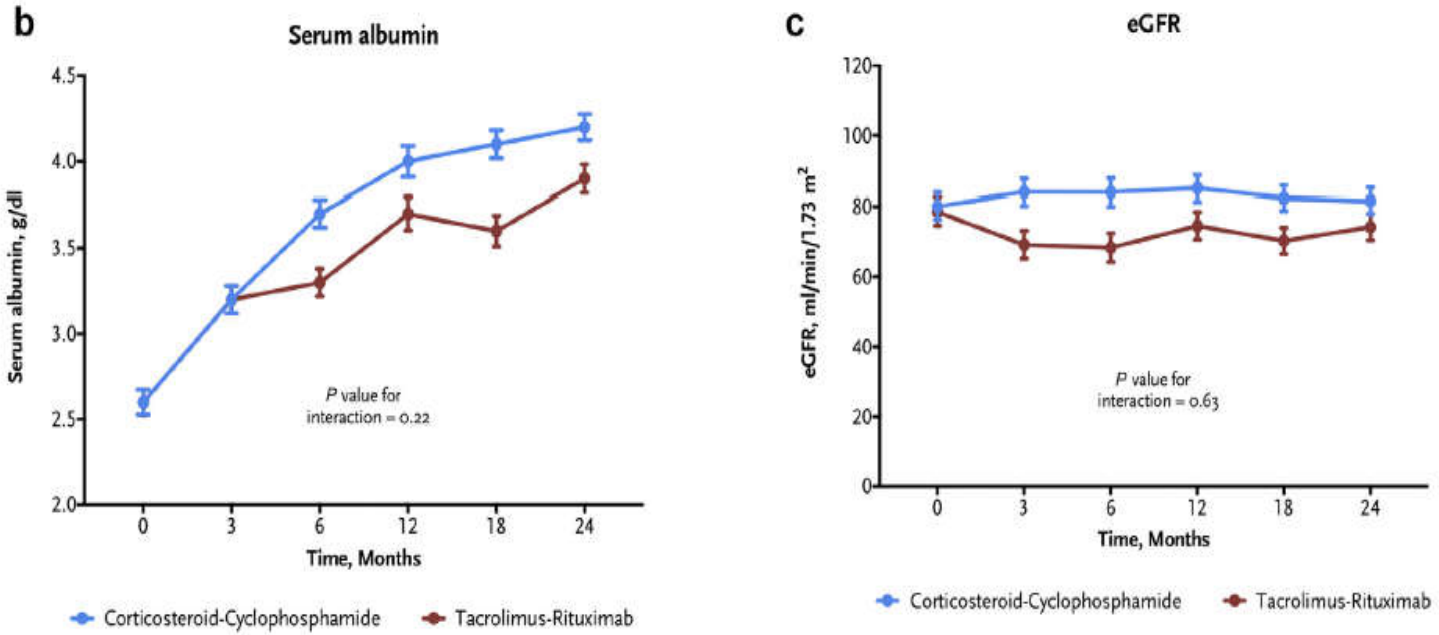


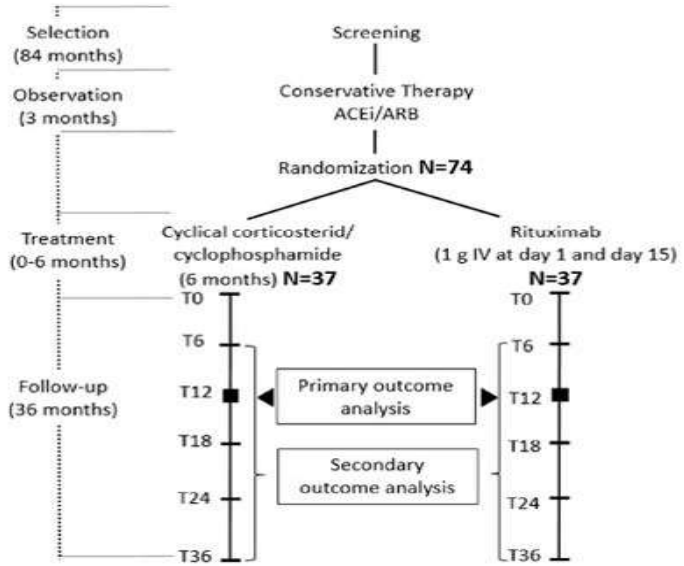
Figure 3| Evolution of proteinuria and anti–phospholipase A2 receptor (PLA2R), serum albumin, and estimated glomerular filtration rate (eGFR). Data are presented as median (interquartile range) over time (albumin, proteinuria, anti-PLA2R) or mean ± SD by assigned treatment.

Kidney International (2021) 99, 986–998

Rituximab or Cyclical Regimen for Membranous Nephropathy

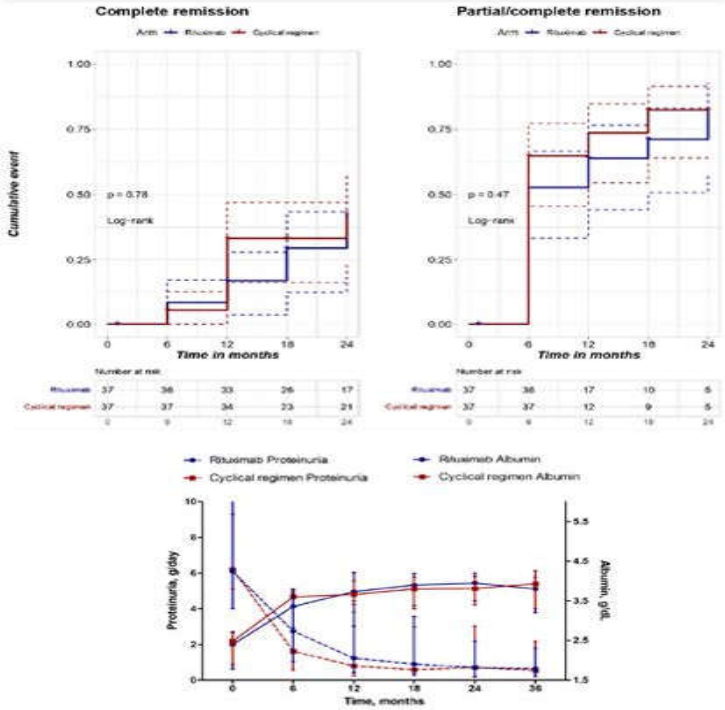
The RI-CYCLO randomized controlled trial

METHODS



74 patients recruited in 84 months

OUTCOME

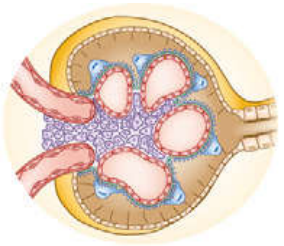


CONCLUSIONS

- Our pilot study shows that completing a larger trial may be challenging.
- While non-significantly different, the point estimate of one-year probability of complete remission was lower in the rituximab arm.
- Throughout the follow-up, the probability to achieve partial or complete remission was similar by study arm.
- The cyclical regimen tended to induce complete remission earlier; rituximab appeared to have a delayed effect.
- The frequency of adverse events was comparable.

doi: 10.1681/ASN.2020071091

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY



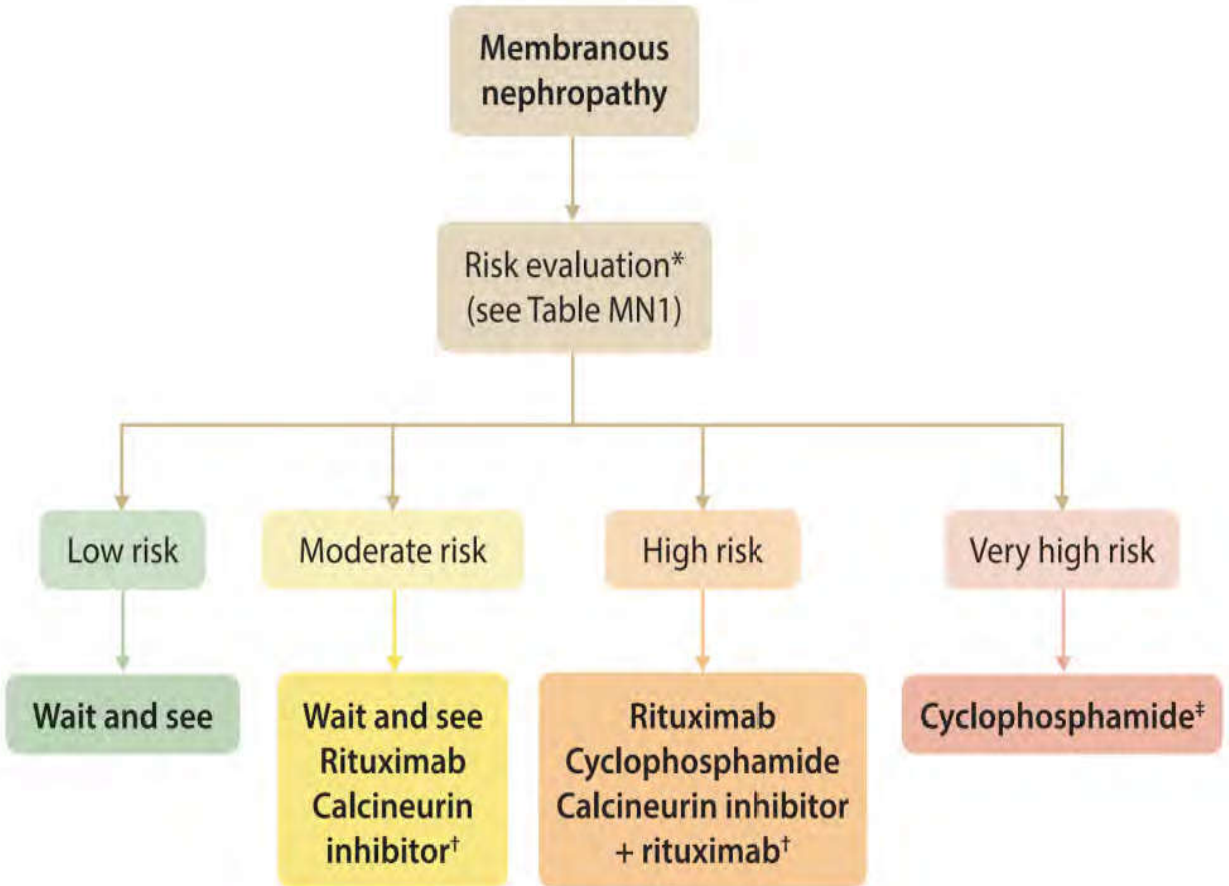
Major randomized clinical trials (RCTs) on membranous nephropathy since 2019.

Table 1. Major randomized clinical trials (RCTs) on membranous nephropathy since 2019.

Study	MENTOR [7]	STARMEN [8]	RI-CYCLO [9]
Design	Multicenter North America $N = 130$	Multicenter Europe $N = 86$	Multicenter Italy+Switzerland $N = 74$
Inclusion	Proteinuria > 5 g/24 h CrCl > 40 mL/min/1.73 m^2	Proteinuria > 4 g/24 h eGFR > 45 mL/min/1.73 m^2	Proteinuria > 3.5 g/24 h eGFR $\geq$ 30 mL/min/1.73 m^2
PLA2R positivity	74% (96/130)	77% (53/69)	66% (59/73)
Run-in	3 months	6 months	3 months
Comparison	Rituximab vs. Cyclosporine	Modified Ponticelli (Methylprednisolone + cyclophosphamide) vs. tacrolimus + rituximab	Modified Ponticelli (Methylprednisolone + cyclophosphamide) vs. Rituximab
Remission definition	CR: proteinuria < 0.3 g/24 h, Alb > 3.5 g/dL PR: proteinuria 50% reduction from baseline + range between 0.3–3.5 g/24 h Relapse: proteinuria > 3.5 g/24 h after CR or PR	CR: proteinuria < 0.3 g/24 h, eGFR > 45 mL/min PR: same as MENTOR, eGFR > 45 mL/min Relapse: same as MENTOR	Same as MENTOR
Outcome CR + PR (CR only)	12 months		
	60% vs. 52%	79% vs. 51%	73% vs. 62% (32% vs. 16%)
	24 months		
	60% vs. 20% (35% vs. 0%)	84% vs. 58% (60% vs. 26%)	81% vs. 85% (35% vs. 42%)
SAE	17% vs. 31%	19% vs. 14%	14% vs. 19%

Results of outcome are given by Intention-To-Treat; PR, partial remission; SAE, severe adverse events.

Risk-based treatment of MN



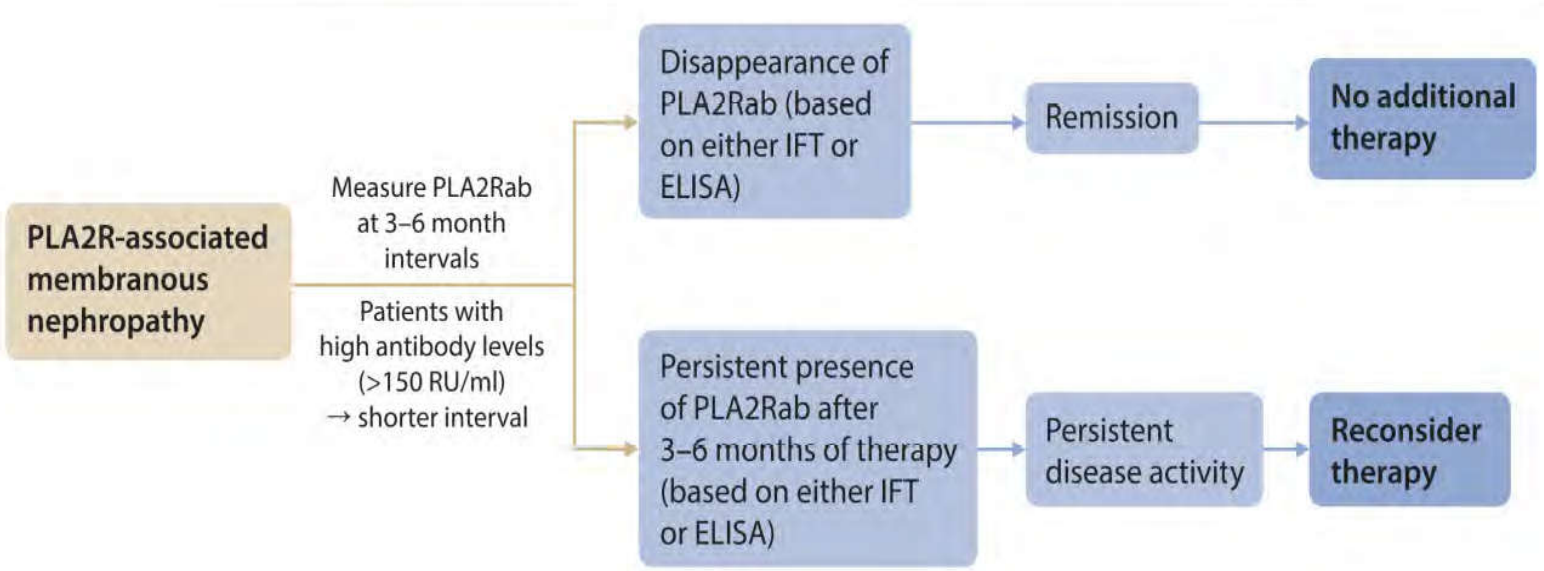
Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, and eGFR >60 ml/min/1.73 m2

Immunosuppressive therapy is not required in patients with MN, nephrotic syndrome, and normal eGFR unless at least one risk factor for disease progression is present or unless serious complications of nephrotic syndrome (e.g., AKI, infections, thromboembolic events) have occurred.

For patients with MN and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and steroids for six months, or tacrolimus-based therapy for at least six months, with the choice of treatment depending on the risk estimate

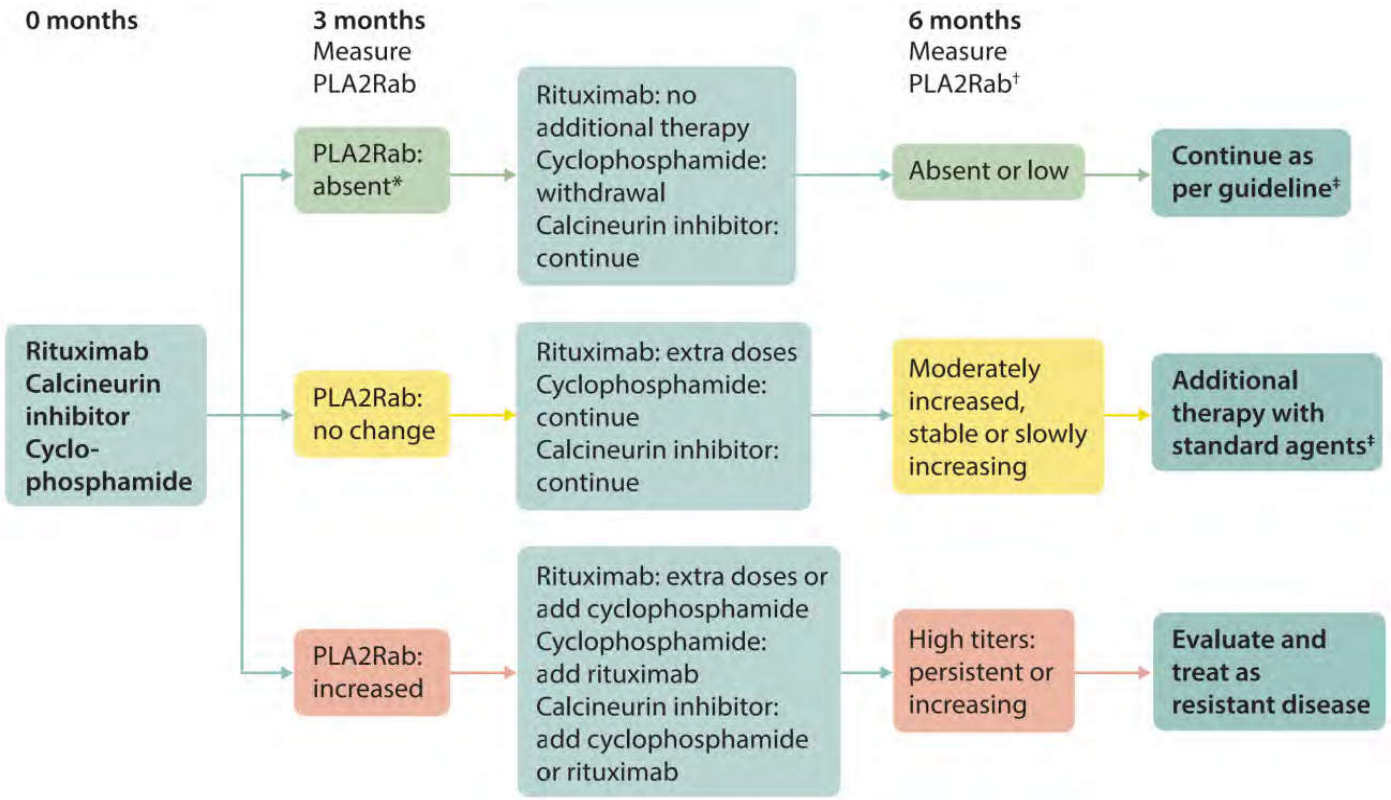
Longitudinal monitoring of PLA2Rab levels at three and six months after start of therapy may be useful for evaluating treatment response in patients with membranous nephropathy, and can be used to guide adjustments to therapy

Guidance for the use and interpretation of the PLA2Rab assay in patients with known PLA2R-associated MN



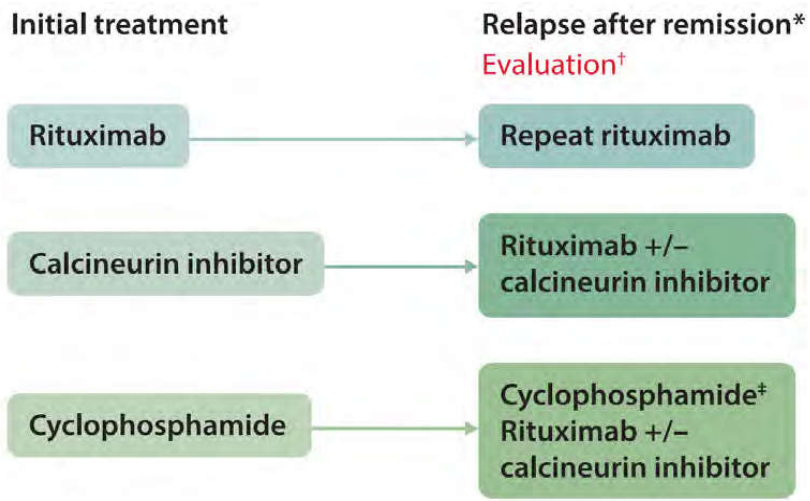
Although there are no defined cut-off values, many experts consider reductions of 50-90% to represent a large decrease in PLA2Rab levels.

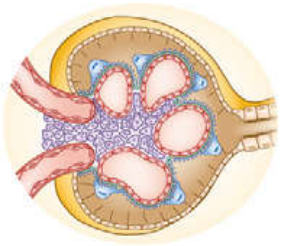
Immunological monitoring in MN after start of therapy



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.

Management of initial relapse after therapy

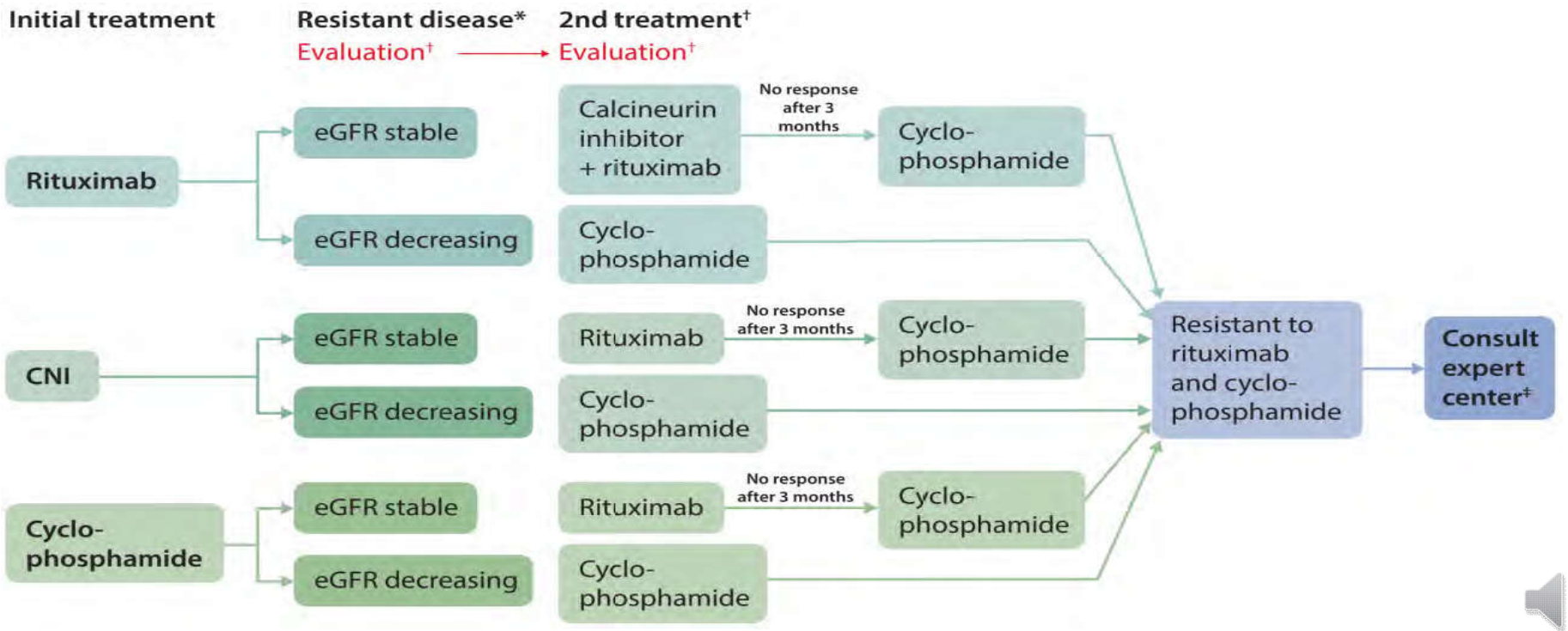




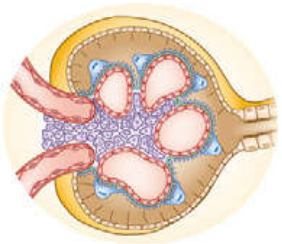
Relapse	increase in proteinuria >3.5 g/day in patients who developed a partial or complete remission
Relapse in patients with a partial remission (characterized by normalization of serum albumin)	an increase of proteinuria paralleled by a decrease in serum albumin levels
Resistance	• persistent NS after immunosuppressive therapy • persistent proteinuria in parallel with persistent or increasing antibody levels
Resistance	in the period of “clinical remission”, PLA2Rab were still positive, this would be evidence for resistant disease
Resistance	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

- 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).
- Disappearance of the antibodies most commonly precedes clinical remission. It is advised to wait at least six to 12 months after antibody disappearance before evaluation of treatment response.

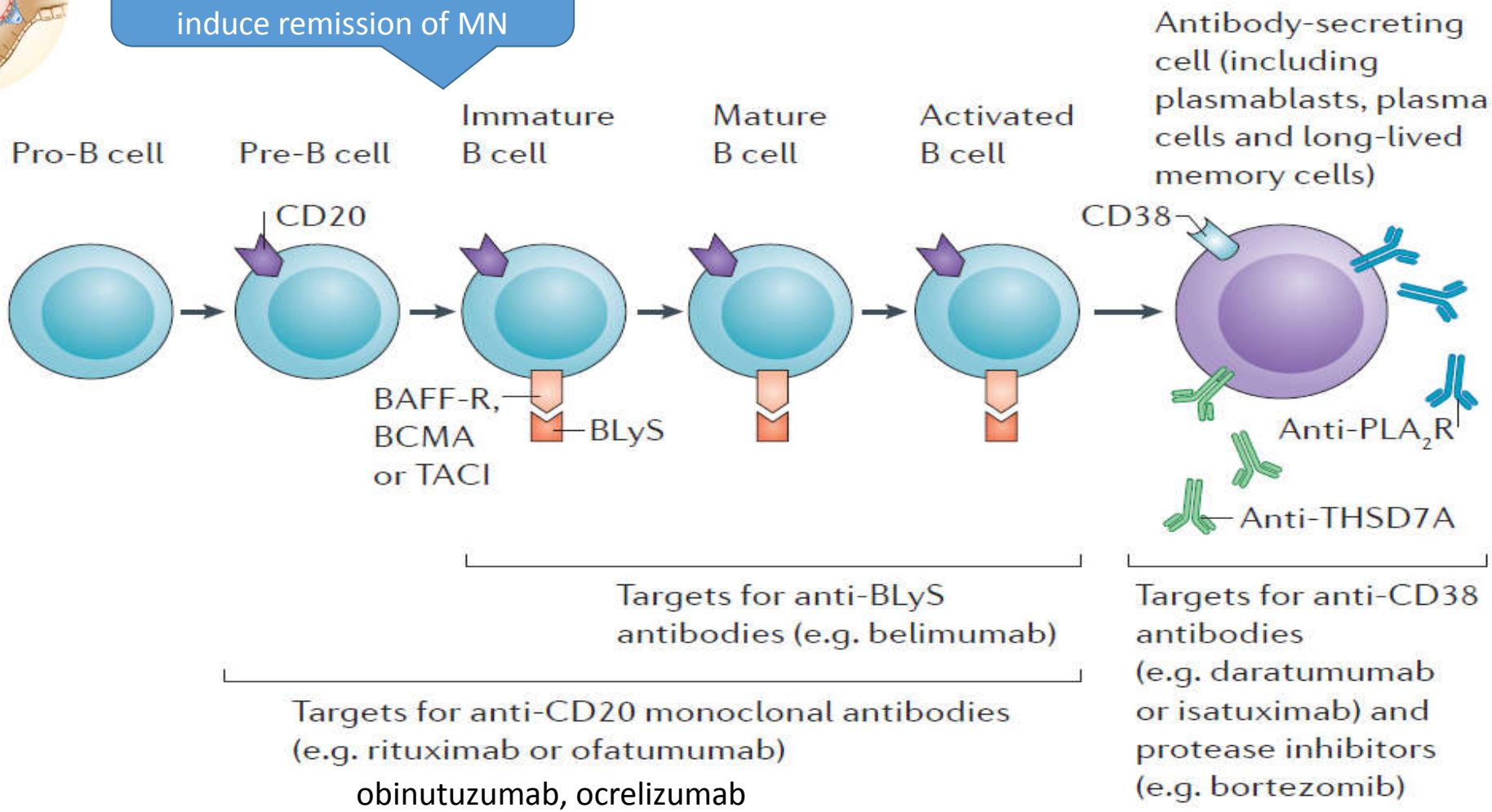
Management of resistant disease



- 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.

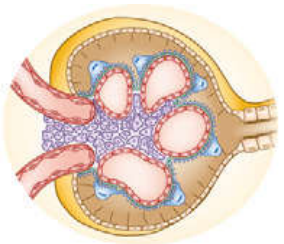


In about 30% to 40% of patients, rituximab fails to induce remission of MN



obinutuzumab, ocrelizumab

Nature review, nephrology, 13(563-579), September 2017



ARTICLE IN PRESS

Case Report

AJKD

Treatment of Membranous Nephropathy in Patients With THSD7A Antibodies Using Immunoadsorption

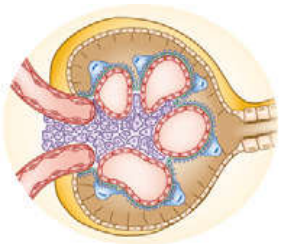
Julia Weinmann-Menke, Stefan Holtz, Daniel Sollinger, Mara Dörken, Simone Boedecker, Beate Schamberger, Frederick Pfister, Kerstin Amann, and Jens Lutz

Antibodies against THSD7A (thrombospondin type 1 domain-containing protein 7A) have been proposed to play a causal role in the development of nephrotic syndrome in patients with THSD7A antibody–positive membranous nephropathy. We hypothesized that removal of these antibodies from plasma could lead to a rapid reduction in proteinuria. Using immunoadsorption to reduce THSD7A antibodies led to a rapid reduction in proteinuria in 2 patients with THSD7A antibody–positive membranous nephropathy. Moreover, our findings support and strengthen the pathogenic role of the antibodies in the development of nephrotic syndrome in patients with THSD7A antibody–positive membranous nephropathy. Taken together, these 2 cases suggest that immunoadsorption could be a useful tool in the treatment of patients with THSD7A antibody–positive membranous nephropathy.

Complete author and article information provided before references.

Am J Kidney Dis. XX(XX): 1-4. Published online Month X, XXXX.

doi: 10.1053/j.ajkd.2019.05.021



nephron
Clinical Practice

Clinical Practice: Case Report

Nephron
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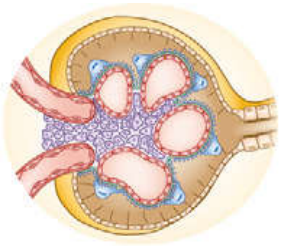
Accelerating the Depletion of Circulating Anti-Phospholipase A_2 Receptor Antibodies in Patients with Severe Membranous Nephropathy: Preliminary Findings with Double Filtration Plasmapheresis and Ofatumumab

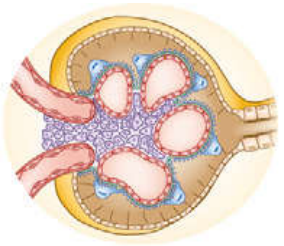
Manuel Alfredo Podestà[a, b] Alessia Gennarini[b] Valentina Portalupi[b]
Stefano Rota[b] Maria Grazia Alessio[c] Giuseppe Remuzzi[a, d] Piero Ruggenenti[a, d]



ACTH (corticotrophin) therapy in resistant primary membranous nephropathy

- ACTH therapy to 11 patients who had failed treatment with other IS treatments
- corticotrophin 40 IU subcutaneous twice a week for 6 months
- >50% reduction in proteinuria
- 2 patients who developed excessive fluid retention and infection

Kidney International (2019) 96, 245–251 251



Treatment of Secondary MN

malignancy-associated MN

treatment of the malignancy
MN can initially be treated supportively

not show evidence of a remission of proteinuria, a trial of immunosuppression following the algorithm for primary MN

The general rule is to treat the underlying disease or stop the offending agent

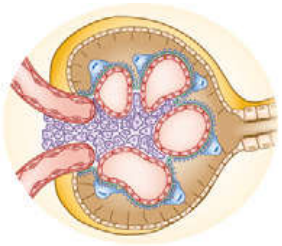
class V lupus nephritis

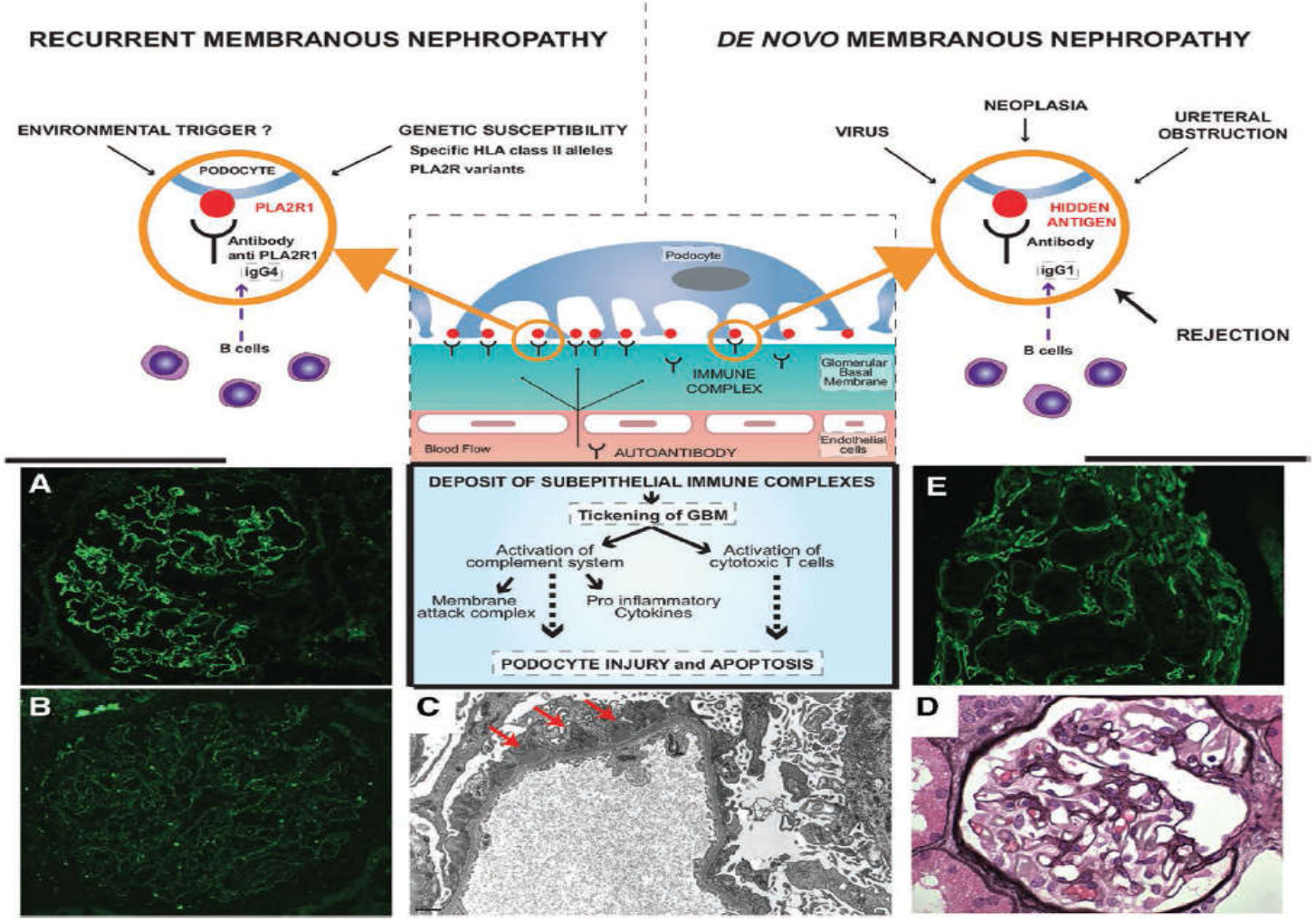
in combination with a proliferative form (class III/IV lupus nephritis)

treatment should be focused on the proliferative classes

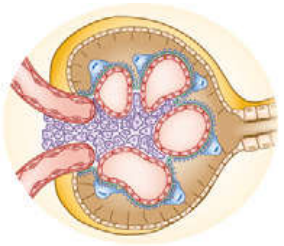
MN due to chronic HBV infection

agents directed against the infection, such as pegylated interferon, entecavir, or tenofovir





Pathophysiology of posttransplant membranous nephropathy. Recurrent membranous nephropathy (rMN) and de novo membranous nephropathy (dnMN)



Clinical and Pathologic Features That Distinguish Recurrent from De Novo MN

Category	Recurrent MN	De Novo MN
Epidemiology	• 10%-45% recurrence rate (higher rates in centers with protocol biopsies) • Clinically apparent by 13-15 mo, but proteinuria can begin within months of transplantation	• 1%-2% posttransplant with increasing incidence with time; reported as ~5.3% at 8 y • Higher incidence in pediatric population, reaching ~9%
Pathogenesis	• Anti-PLA_2R at time of transplantation is a risk factor • Can appear years later with reemergence of autoantibodies when transplant immunosuppression decreased	• Not fully known • Has been associated with chronic and/or antibody-mediated rejection
Clinical presentation	• Similar to primary MN • May be detected earlier with lower amounts of proteinuria due to heightened surveillance (especially with protocol biopsy)	• Can be asymptomatic or with various degrees of proteinuria many years after transplantation
Diagnosis	• MN present on biopsy of native kidney • Presence of anti-PLA_2R can support recurrent MN if native diagnosis not known • Positive PLA_2R staining within deposits in 70%-80% • IgG4 is the dominant or codominant IgG subclass	• Diagnosis other than MN in biopsy of native kidney • Typically not associated with anti-PLA_2R antibody or PLA_2R staining of deposits • Evidence of chronic and/or antibody-mediated rejection • IgG1 is predominant IgG subclass
Treatment	• Can closely follow if low titer anti-PLA_2R, subnephrotic proteinuria, stable kidney function • Transplant immunosuppression may cause decrease and disappearance of autoantibodies • Heightened concern warranted as process already resulted in loss of native kidneys • Rituximab for worsening disease in setting of transplant immunosuppression	• Unknown natural history but 50% graft loss has been reported • Treat underlying rejection and implement antiproteinuric therapy • Increase maintenance immunosuppression, consider plasmapheresis if chronic rejection is present • Consider rituximab or cyclophosphamide if kidney function is rapidly declining

IgG, immunoglobulin G; MN, membranous nephropathy; PLA_2R, phospholipase A_2 receptor.

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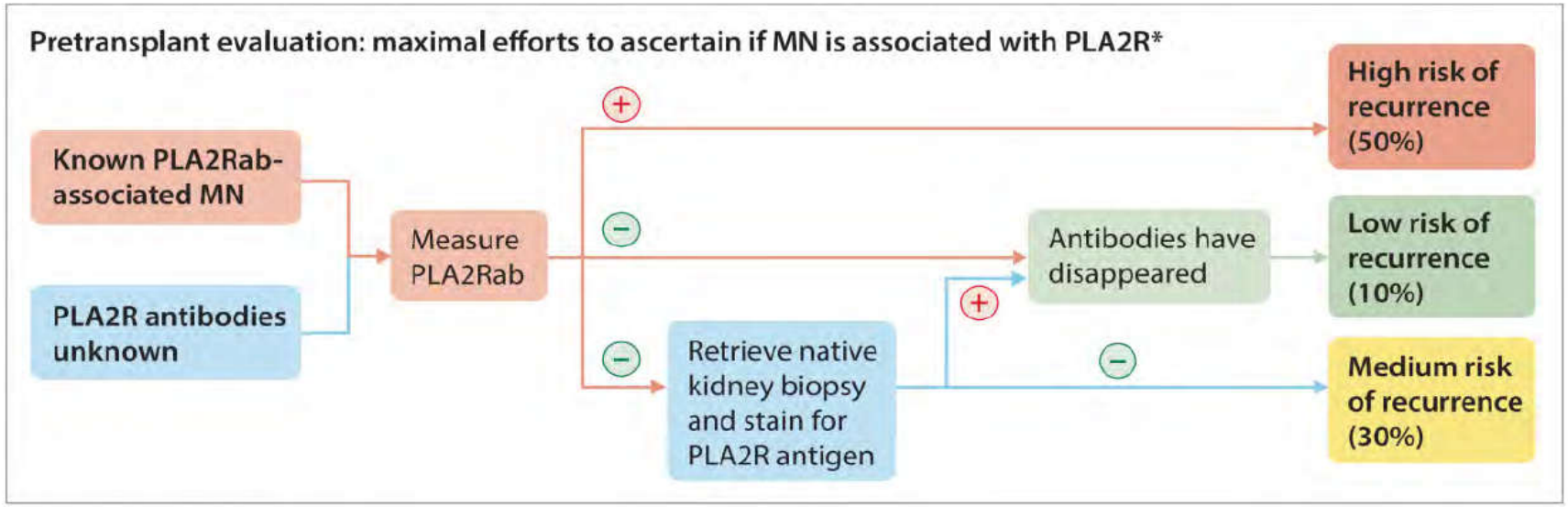
Evaluation of a kidney transplant recipient with MN



Discuss recurrence rate:

- Recurrence risk depends on the evaluation of the causative antibodies
- Recurrence risk may be higher after living related donor transplantation, but the benefits of living donor donation outweigh the possible harm of disease recurrence

In patients with MN not associated with PLA2Rab, proteinuria should be evaluated monthly for at least six to 12 months after transplantation.

- A kidney biopsy is needed when proteinuria exceeds 1g/d

In patients with PLA2R-associated MN, regular measurement of anti PLA2Rab after kidney transplantation is advised in the first six to 12 months after transplantation. The frequency of monitoring may vary from once per month in patients with high titers pretransplant to once per three months in patients without measurable antiPLA2Rab pretransplant

- A relapse can be anticipated with persistently high or increasing titers of antiPLA2Rab, and in such cases performing a kidney biopsy in patients with proteinuria 0.3 to 1.0 g/d can be considered

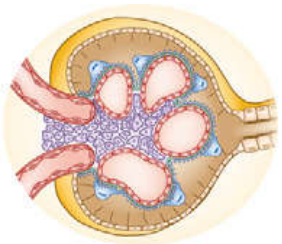
Peri- and post-transplant monitoring:

- Measure proteinuria every month → if proteinuria 1 g/d→ biopsy of kidney
- In patients with known PLA2Rab-associated MN: measure PLA2Rab every 1–3 months depending on pretransplant antibody status
  → PLA2Rab increasing → increased likelihood of recurrence, consider early kidney biopsy
  → PLA2Rab decreasing →lower likelihood of recurrence, perform kidney biopsy only if clinically indicated

Treatment of recurrence:

- Treat with angiotensin-converting enzyme inhibitor/angiotensin II-receptor blocker
- Optimize immunosuppressive therapy, therapeutic drug monitoring of mycophenolate mofetil aiming at AUC > 50 mg*hr/L
- Proteinuria <1 g/d →evaluate/monitor at 1–3 month intervals
- Proteinuria >1 g/d →rituximab 1 g at day 1 and day 15

studies have suggested that higher PLA2Rab levels (>45 RU/ml) are associated with increased risk



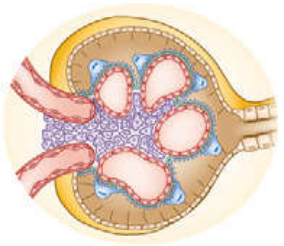
Original Clinical Science

Recurrent Membranous Nephropathy After Kidney Transplantation: Treatment and Long-Term Implications

Ayelet Grupper, MD,[1] Lynn D. Cornell, MD,[2,3] Fernando C. Fervenza, MD,[1,2] Laurence H. Beck, Jr, MD,[4] Elizabeth Lorenz, MD,[1,2] and Fernando G. Cosio, MD[1,2]

Background. Membranous nephropathy (MN) can recur in kidney allografts leading to graft dysfunction and failure. The aims of these analyses were to assess MN recurrence, clinical and histologic progression, and response to anti-CD20 therapy. **Methods.** Included were 63 kidney allograft recipients with biopsy proven primary MN followed up for 77.0 (39-113) months (median, interquartile range). Disease recurrence was diagnosed by biopsy (protocol or clinical), and follow-up was monitored by laboratory parameters and protocol biopsies. **Results.** Thirty of 63 patients (48%) had histologic recurrence often during the first year. In 53% of the cases, recurrence was diagnosed by protocol biopsy. Recurrence risk was higher in patients with higher proteinuria pretransplant [hazard ratio = 1.869 (95% confidence interval, 1.164-3.001) per gram, $P = 0.010$] and those with anti-phospholipase A2 receptor antibodies [hazard ratio = 3.761 (1.635-8.652), $P = 0.002$]. Thirteen patients with recurrence had no clinical progression, and in 2, MN resolved histologically. Seventeen of 63 patients (27%) had progressive proteinuria and were treated with anti-CD20 antibodies, resulting in complete response in 9 (53%), partial response in 5 (29%), and no response in 3 (18%). Posttreatment biopsies were obtained in 15 patients and showed histologic resolution in 6 (40%). Disease recurrence did not correlate with graft survival. However, 5 of 11 (45.4%) graft losses were due to recurrent MN. Death-censored graft survival in MN did not differ from that of 273 control recipients with autosomal dominant polycystic kidney disease. **Conclusions.** Membranous nephropathy recurs in 48% of cases threatening the allograft. Treatment of early but progressive recurrence with anti-CD20 antibodies is quite effective achieving clinical remission and histologic resolution of MN.

(*Transplantation* 2015;00: 00–00)



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Original Report: Transplantation

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Single-Dose Rituximab for Recurrent Glomerulonephritis Post-Renal Transplant

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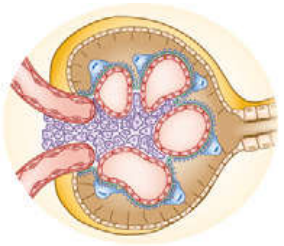
Rowena B. Delos Santos[b] Christina L. Klein[b] Daniel C. Brennan[b]

[a]Department of Pharmacy, Barnes-Jewish Hospital, and [b]Renal Division, Department of Internal Medicine, Washington University School of Medicine, Saint Louis, Mo., USA

Single-dose rituximab for treatment of recurrent GN was associated with less subsequent rejection and longer time to graft loss without increased infection, but was no more effective than regimens not using rituximab at 36-months except those with recurrent membranous GN.



EARLY TREATMENT WITH RITUXIMAB IN RECURRENT MEMBRANOUS NEPHROPATHY AFTER KIDNEY TRANSPLANT:

Nikhil Agrawal1, Sreedhar Adapa2, Venu Madhav Konala3, Hemant Dhingra2, Martha Pavlakis1. 1Beth Israel Deaconess Medical Center, Boston, MA, United States; 2The Nephrology Group, Fresno, CA, United States; 3Ashland Bellefonte Cancer Center, Ashland, KY, United States

Treatment with rituximab early in the disease course appears to be effective and perhaps necessary given less likelihood of spontaneous remission

NKF 2019 Spring Clinical Meetings, AJKD Vol 73 | Iss 5 | May 2019

Prophylactic anticoagulant therapy in patients with membranous nephropathy and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications

- The risk of thrombosis is particularly increased in the first six-to-twelve months after onset of disease.
- the VTE risk starts to increase at a serum albumin level lower than 2.8 g/dL and increases further with lower values.
- Patients with membranous nephropathy and nephrotic syndrome are also at risk of developing arterial thrombotic events. The risk of arterial thrombotic event is dependent on age, history of previous events, diabetes, eGFR, smoking, and severity of nephrotic syndrome
- Use of aspirin is insufficient to prevent VTE; use of warfarin is sufficient to prevent ATE
- A good alternative is to use low-dose LMW heparin + aspirin for a period of three months before switching to warfarin, allowing to judge the course of proteinuria
- the use of direct oral anticoagulant agents such as apixaban for prophylaxis needs further study.

Anticoagulant therapy in patients with MN