Rituximab in MGN

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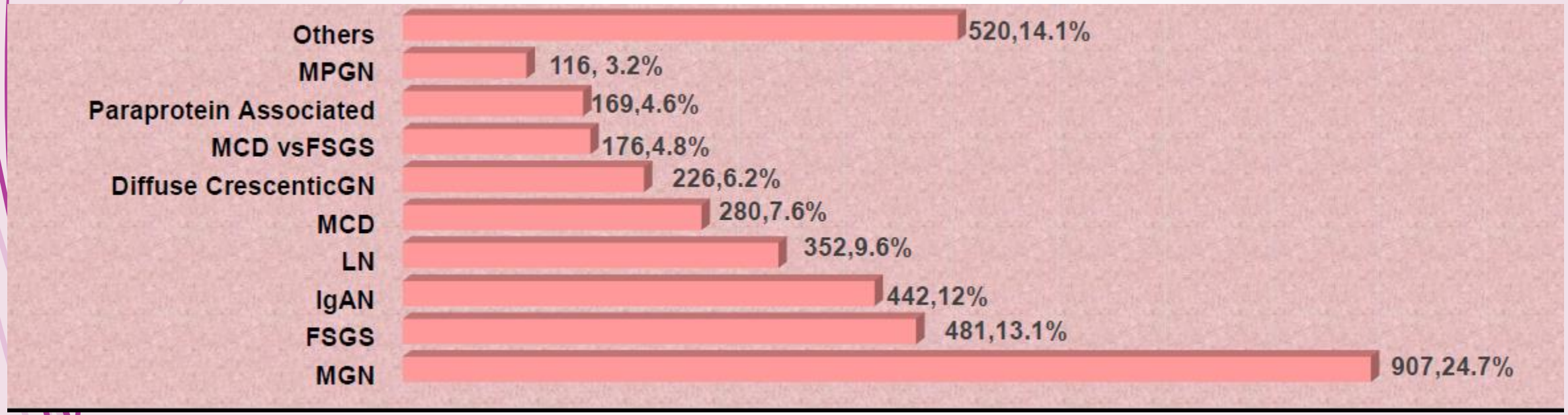
Membranous Nephropathy (MN)

- Membranous nephropathy is among the most common causes of primary nephrotic syndrome in adults.



3680 Kidney Biopsy cases

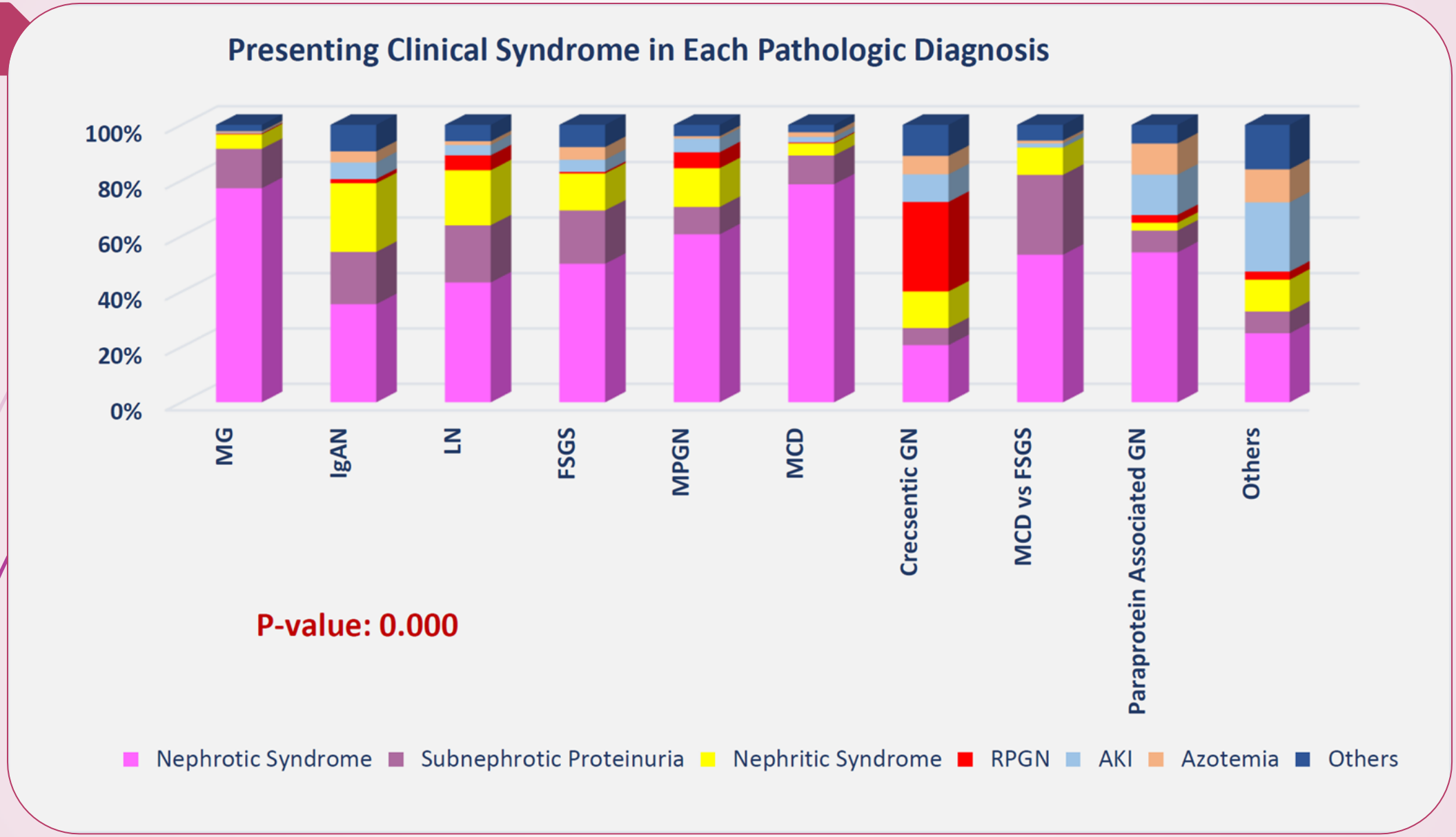
Bagherzadegan H, Ossareh S, Asgari M. WCN Abstracts 2017

Demographic and clinical manifestations of the main pathologic diagnoses

Pathologic Diagnosis	MGN	FSGS	IgAN	LN	MCD	Crescentic GN	MCD vs FSGS	Paraprotein Associated	MPGN	Others	Total	p-value
Frequency (%)	998 (24.9%)	527 (13.2%)	482 (12%)	374 (9.3%)	300 (7.5%)	242 (6%)	195 (4.9%)	179 (4.5%)	122 (3%)	582 (14.5%)	4001 (100%)	
Mean age ±SD	40.4± 15.3	39.2±15.9	36.9±12.9	31.1±11.3	33.2±15.1	43.1±17.3	36.5± 14.9	54.3± 15.8	34.1± 17.5	44.1±17.6	39.4±16.1	<0.001
Male: Female	1.3: 1	1.5: 1	2.6: 1	1: 3.7	1.1: 1	1.2: 1	1: 1	1.5: 1	1.5 : 1	1.6: 1	1.3: 1	<0.001
NS (%)	79.6	54.9	49	54.2	81.9	48.3	57.8	69.4	75.9	40.3	61.6	<0.001
SCr≥ 1.4 (%)	22	54.3	65.1	48	27.5	95.4	35.4	71.9	62.3	85.9	52.2	<0.001
Hypertension(%)	34.3	47.7	51.2	44.6	24.7	57.8	27.4	34.9	63.6	59.5	43.9	<0.001

Bagherzadegan H, Ossareh S, Asgari M. ERA- EDTA Abstracts 2018

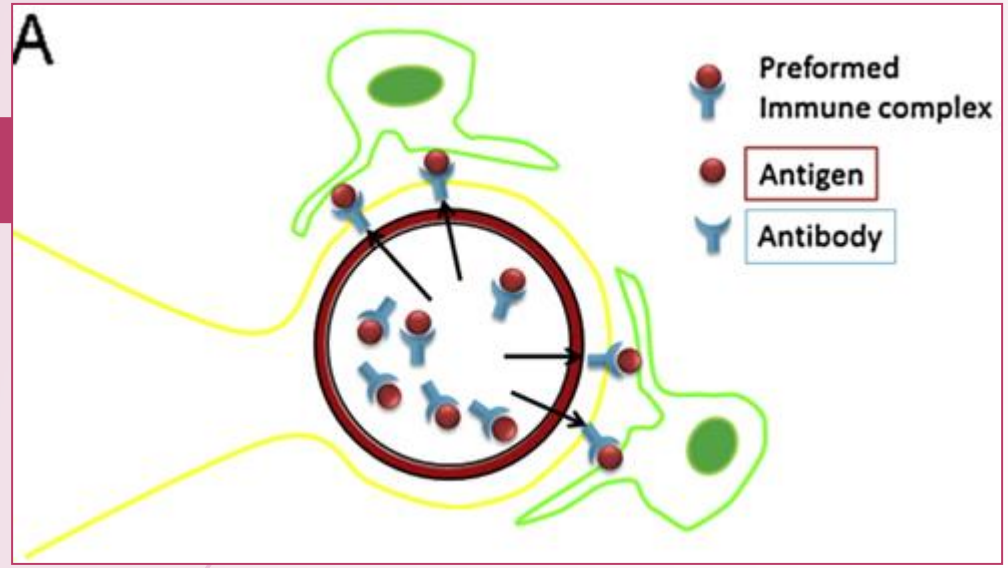
Presentation



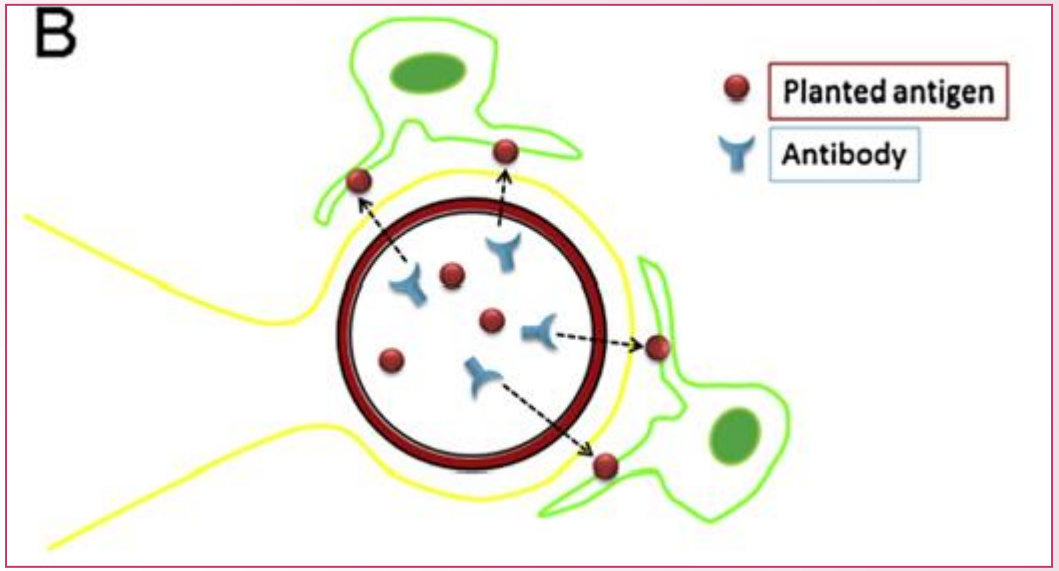
Bagherzadegan H, Ossareh S, Asgari M. ERA- EDTA Abstracts 2018

It is characterized by basement membrane thickening with little or no cellular proliferation or infiltration, and the presence of electron dense deposits across the glomerular basement membrane, together with fine granular subepithelial IgG and C3 deposits.

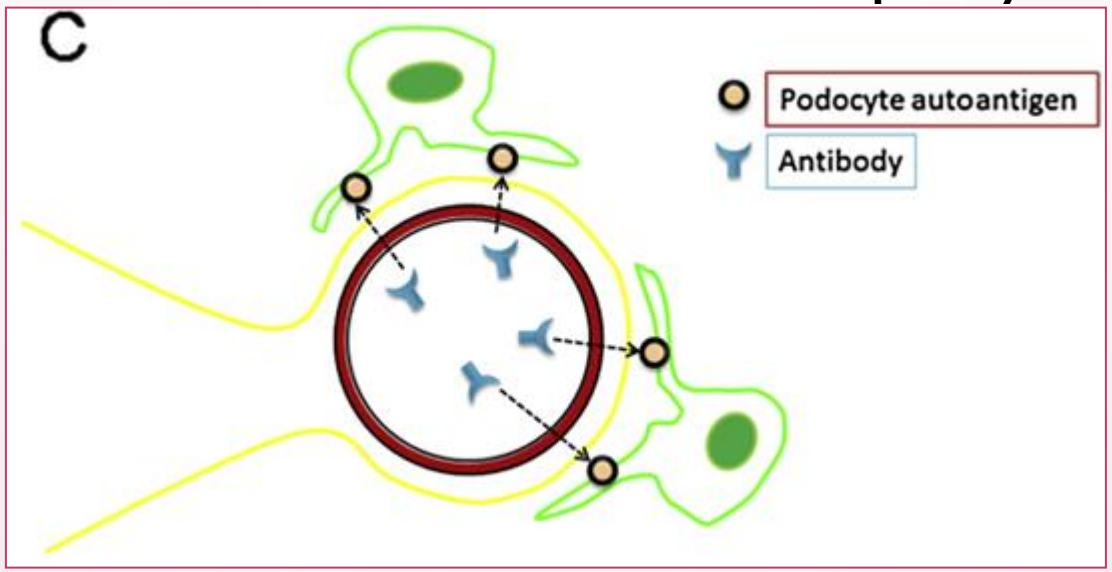
Pathogenesis of MN



The passive entrapment of preformed immune complexes



Planted antigens. The circulating pathogenic Ags are localized, or planted, in the SE sites, which subsequently form in situ IC deposits with Abs.



Podocyte autoantigen

Lai WL. J Formos Med Assoc. 2015;114:102

Podocyte Auto Ags

- Many cases of idiopathic membranous nephropathy may be due to autoantibodies directed against podocyte Ags:

1. Anti PLA2 Ab* (70%) **Beck LH Jr. NEJM. 2009;361:11**
2. THSD7A** Ab(3-10%) **Tomas NM. NEJM 2014; 371:2277** (Also positive in malignancy related MGN)
3. Anti-NEP+ antibodies **Debiec H. NEJM. 2002;346:2053** (responsible for antenatal MN)
4. Intracellular podocytye Ags: Alpha-enolase, aldose reductase, and superoxide dismutase 2 **Murtas C. Clin J Am Soc Nephrol. 2012;7:1394**
5. Abs to Cationic form of bovine serum albumin (BSA) **Debiec H. NEJM 2011;364:2101.**

*Phospholipase A2 receptor; **(Thrombospondin Type-1 Domain-Containing 7A); +Neutral Endopeptidase

Secondary MN

- Includes hepatitis B antigenemia, autoimmune diseases, thyroiditis, carcinoma, and the use of certain drugs such as NSAIDs, penicillamine, gold, and captopril.

- **Antigens:**
  1. Double-stranded DNA in systemic lupus erythematosus
  2. Thyroglobulin in thyroiditis
  3. Hepatitis B antigen, treponemal antigen,
  4. *Helicobacter pylori* in the relevant infections;
  5. Carcinoembryonic antigen
  6. Prostate-specific antigen in malignancy.

Role of T cells

- T helper cells activate different immune effector mechanisms and appear to play a role in the pathogenesis of glomerulonephritis and may also participate in the genesis of proteinuria in MN.
- The T helper subset Th1 tends to predominate in proliferative and crescentic forms of glomerulonephritis, whereas Th2 predominates in MN and minimal change disease.

Genetic Factors

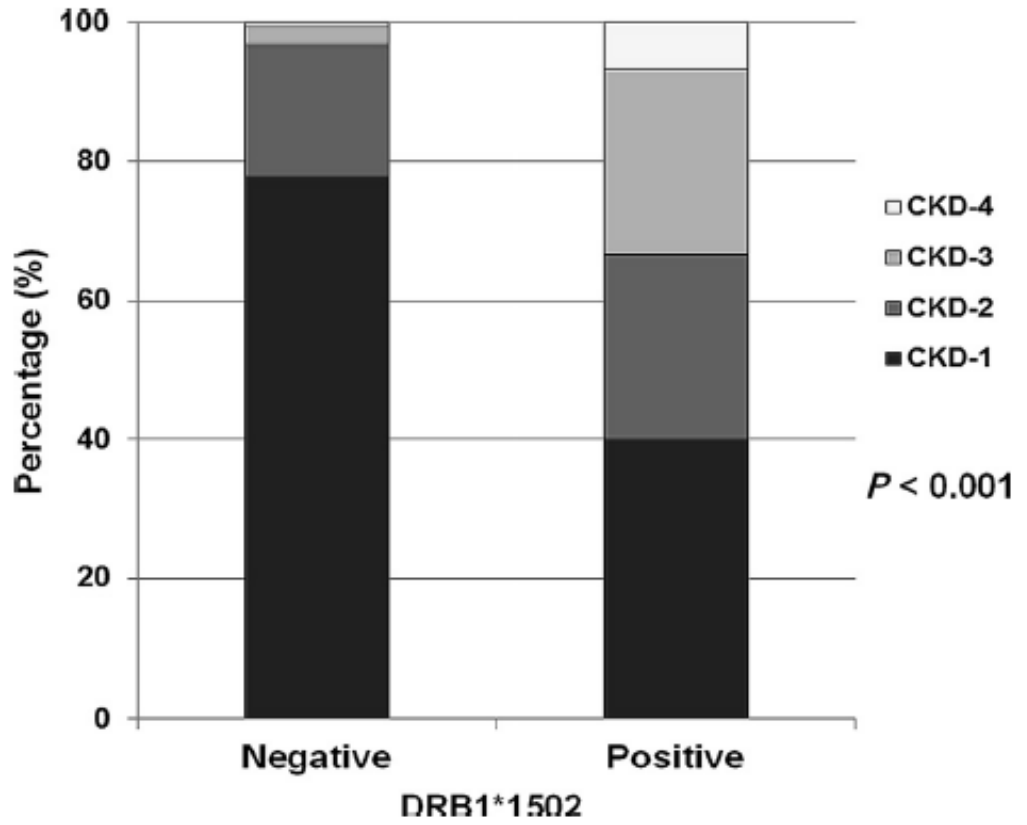
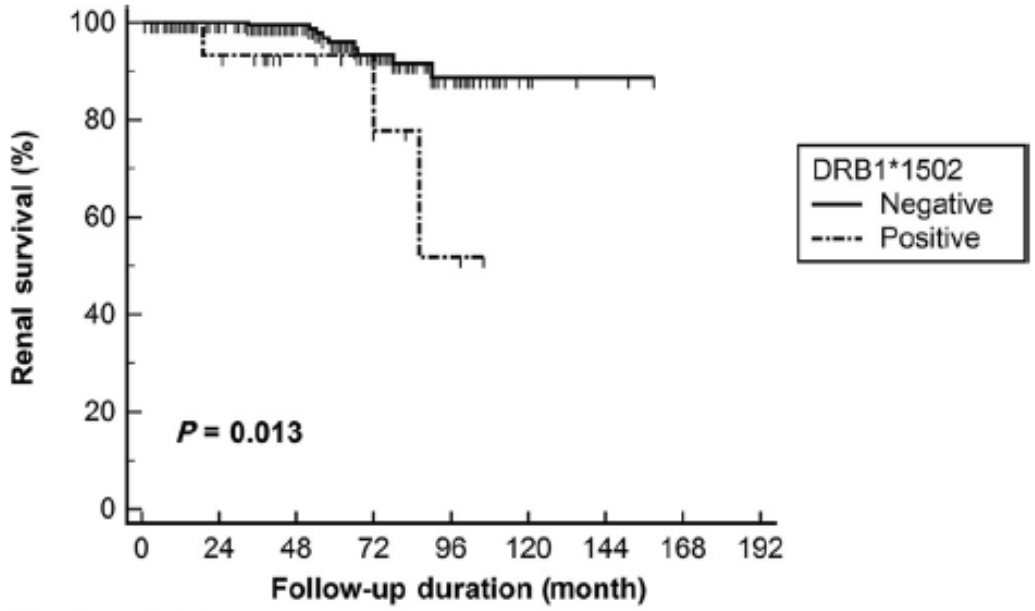


Figure 2 | Comparison of chronic kidney disease (CKD) stages in primary membranous nephropathy patients with versus without the human leukocyte antigen class II allele DRB1*1502.



Number at risk

DRB1*1502 negative	243	210	129	63	24	4	2	0
DRB1*1502 positive	15	14	8	4	2	0	0	0

Figure 4 | Kaplan–Meier renal survival curves (end-stage renal disease) in primary membranous nephropathy patients. Patients with human leukocyte antigen DRB1*1502 had worse kidney outcomes during follow-up ($P = 0.013$).

Wang H. KI.2018: 974–982

Terminology

- The term IMN should now be superseded by the term primary or autoimmune MN (AMN) (anti-PLA2R or anti-THSD7A positive) classifying about 80% to 90% of cases previously designated IMN.
- Some patients who are low producers of antibody may appear to be seronegative until the antibody has saturated the PLA2R binding sites on podocytes and only then become seropositive
- In practical terms, the high affinity of anti-PLA2R means that PLA2R tissue positivity (PLA2R antigen in the glomerular basement membrane immune complexes) can account for 80% to 90% of cases, including those showing low or even absent seropositivity.

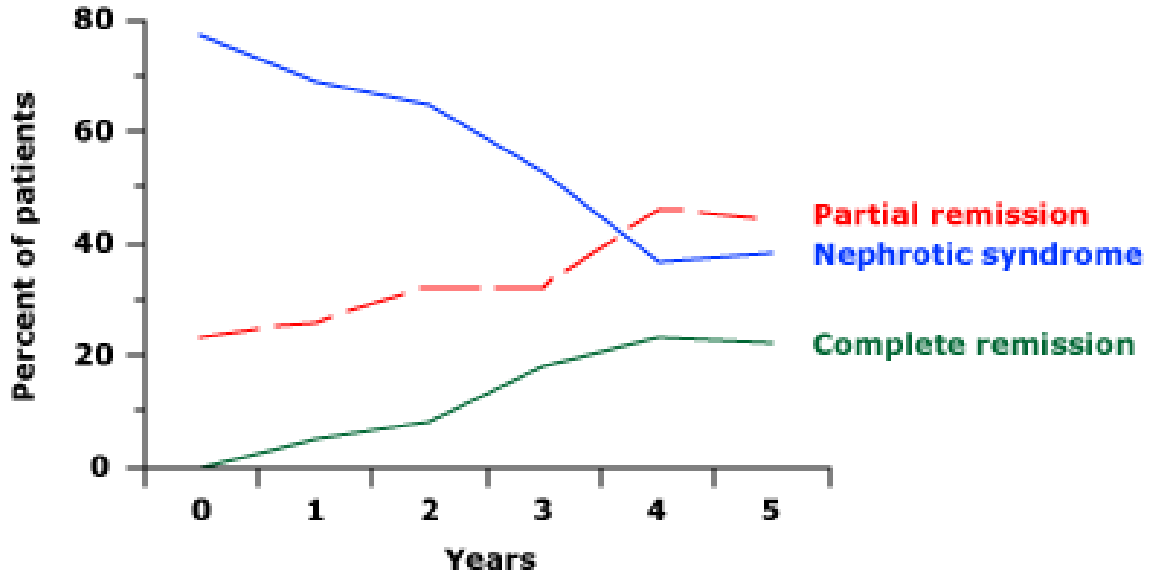
Catran DC. KI. 2017: 566–574

Course of MN

- MN is a chronic disease, and its course includes spontaneous remissions (in ~ 30% of patients, usually within the first 2 years after diagnosis in those with milder presentations) and frequent relapses.

- Nephrotic patients who do not go into remission are likely to progress to end-stage renal disease.

High incidence of remission in untreated membranous nephropathy



Course of 100 consecutive untreated patients with idiopathic membranous nephropathy. Over a five-year period, there was a progressive increase in the incidence of partial or complete remission, while the incidence of the nephrotic syndrome fell.

Data from: Schieppati A, Mosconi L, Perna A, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med 1993; 329:85.

Risk of progression to a creatinine clearance (CrCl) ≤60 mL/min per 1.73 m^2 during a follow-up> 5yrs

- Proteinuria **<3.5 g/day** and stable normal renal function over 6 months: **6%**
- Proteinuria of **12 g/day**, and a CrCl on presentation of 96 mL/min, which declines to 78 mL/min by 6 months: **72%**

Cattran DC. KI. 1997:901

Risk of progression to a creatinine clearance (CrCl) ≤60 mL/min per 1.73 m^2 during a follow-up> 5yrs

- **Low risk:** Proteinuria remains <4 g/day and CrC remains normal for a 6-month follow-up (**< 8% risk** of developing chronic renal insufficiency over 5 years.)
- **Moderate risk:** Proteinuria is 4- 8 g/day and persists for > 6 months and CrC is normal or near normal and remains stable over 6 months. (**50%** risk of developing chronic renal insufficiency over 5 years.).
- **High risk:** Proteinuria> 8 g/day and persists for 3 months and/or renal function that is either below normal (and considered due to MN) or decreases during the observation period. (**75%** risk of developing chronic renal insufficiency over 5 years.).

https://www.uptodate.com/contents/treatment-of-idiopathic-membranous-nephropathy?csi=b24a2b8f-fd8b-4300-9456-e93a504e331d&source=contentShare

KDIGO GN 2012

Table 14 | Definitions of complete and partial remission in IMN

Complete Remission: Urinary protein excretion <0.3 g/d (uPCR <300 mg/g or <30 mg/mmol), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration, and a normal SCr.

Partial Remission: Urinary protein excretion <3.5 g/d (uPCR <3500 mg/g or <350 mg/mmol) ***and*** a 50% or greater reduction from peak values; confirmed by two values at least 1 week apart, accompanied by an improvement or normalization of the serum albumin concentration and stable SCr.

MN, membranous nephropathy; uPCR, urine protein:creatinine ratio.
See also Chapter 1.
Based on previously published information, Jha *et al.* and Passerini *et al.*[204,205]

KI Supplements 2012: 186-197

KDIGO guideline recommends to start initial therapy only in patients

- With nephrotic syndrome **AND** when at least one of the following conditions is met:

1. Urinary protein excretion persistently >4 g/d **AND**
   Remains at over 50% of the baseline value, **AND**
   Does not show progressive decline, during antihypertensive and antiproteinuric therapy
   for at least 6 months; (1B)
2. The presence of severe, disabling, or life threatening symptoms related to the nephrotic syndrome; (1C)

KI Supplements 2012: 186-197

Initial Conservative therapy

- Conservative therapy is recommended to be instituted at the earliest phase of MN.
- This may potentially eliminate the need for subsequent IS in low risk of progression patients with
  1. Low-level proteinuria <4 g/day,
  2. Well-preserved renal function,
- In includes:
  1. Renin-angiotensin system blockade,
  2. Diuretics for edema
  3. Diet (low salt)
  4. Lipid lowering
  5. Anticoagulation (Alb. <2.2 g/dL) (**Lai WL. J Formos Med Assoc. 2015 Feb;114:102)**
- Failure to adhere to sodium restriction can significantly mute the benefits of conservative treatment even if the immunologic injury has dissipated. **(Barnes CE Nephron Clin Pract. 2011;119:c145–c153.)**

Cattran DC. KI. 2017: 566–574

If Initial Conservative

Therapy is not

Completely Effective

Therapies not recommended by KDIGO as the initial therapy

- Cosrticosteroids Alone
- Mycofenolate Mofetil
- ACTH

Calcineurin inhibitors

- Both cyclosporine and tacrolimus have proven efficacy in patients with idiopathic MN.
- Cyclosporine plus low-dose prednisone (maximum of 10 mg/day) is effective in inducing remission of proteinuria and in preventing progression to end-stage renal disease.

Kidney International, Vol. 59 (2001), pp. 1484–1490

Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial

DANIEL C. CATTRAN, GERALD B. APPEL, LEE A. HEBERT, LAWRENCE G. HUNSICKER, MARC A. POHL, WENDY E. HOY, DOUGLAS R. MAXWELL, and CHERYL L. KUNIS, for the NORTH AMERICAN NEPHROTIC SYNDROME STUDY GROUP

Department of Medicine, University of Toronto, Toronto, Ontario, Canada; Departments of Medicine, Columbia Presbyterian Medical Center, New York, New York, Ohio State University, Columbus, Ohio, University of Iowa Hospitals, Iowa City, Iowa, Cleveland Clinic Foundation, Cleveland, Ohio, Lovelace Medical Foundation, Albuquerque, New Mexico, and Indiana University School of Medicine, Indianapolis, Indiana, USA

Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial.

Background. A clinical trial of cyclosporine in patients with steroid-resistant membranous nephropathy (MGN) was conducted. Although MGN remains the most common cause of

Membranous nephropathy (MGN) is the most common cause of adult-onset idiopathic nephrotic syndrome. Although the overall renal survival percentage remains high at 10 years, its incidence rate results in the disease

Cattran DC. KI, 2001: 1484–1490

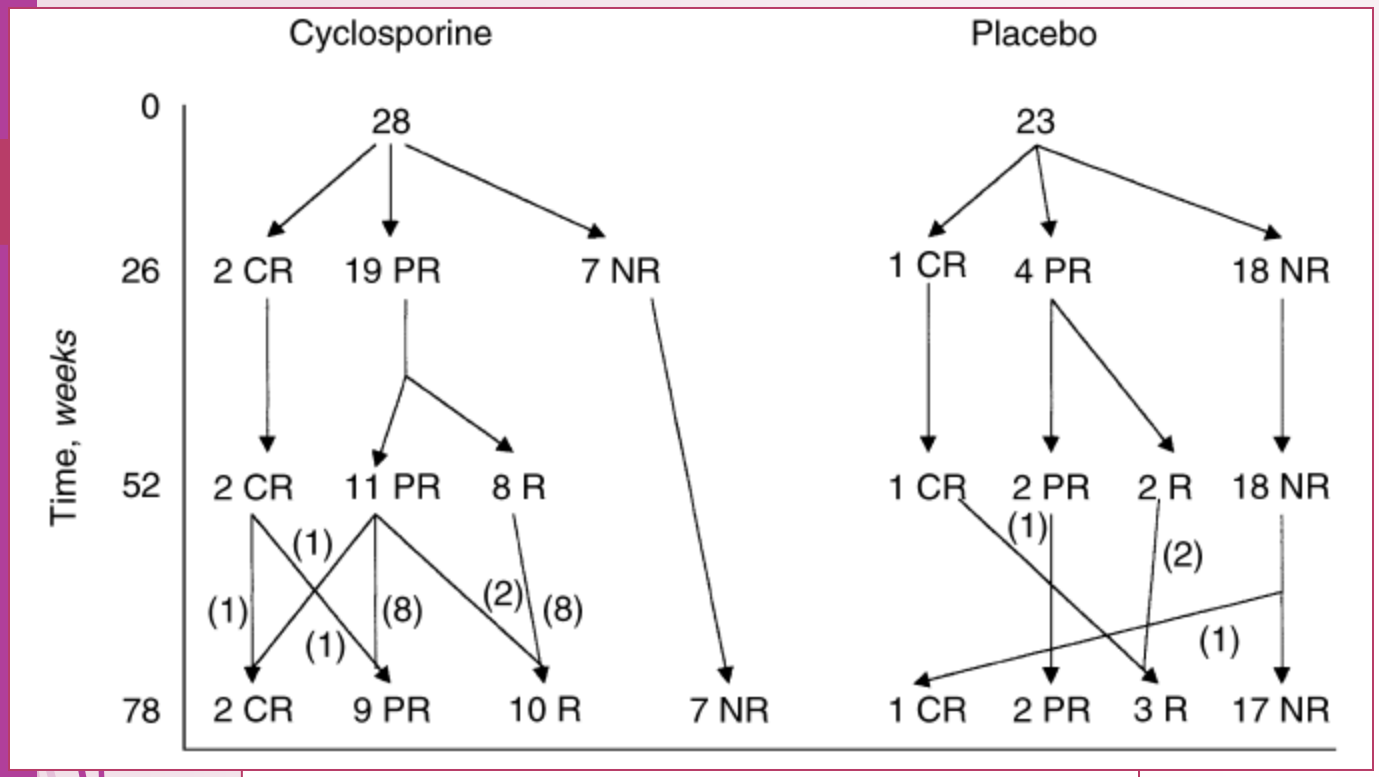


Fig. 2. Remission and relapses in the two groups over the study and follow-up period. Abbreviations are: CR, complete remission; PR, partial remission; NR, no remission; R, relapse.

Adverse effects:
HTN (development in 8 and worsening in 2)
Nausea: 4

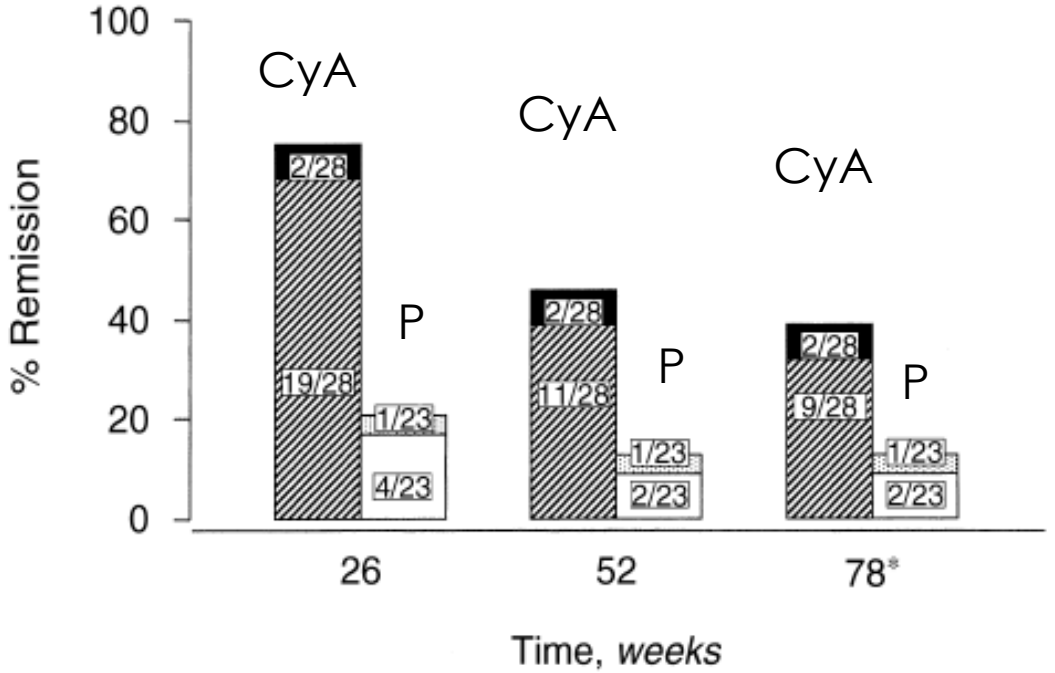


Fig. 1. Remissions in proteinuria in the cyclosporine patients [(▨) partial, (■) complete] compared with the placebo-treated [(⊡) complete, (□) partial] at different time points of the study. At week 26, $P = 0.001$; at week 52, $P = 0.004$; and week 78, $P = 0.007$. Early stops (*) were assessed at the last follow-up.

Nephrol Dial Transplant (2006) 21: 3127–3132
doi:10.1093/ndt/gfl360
Advance Access publication 12 September 2006

NDT
Nephrology Dialysis Transplantation

Original Article

Induction and long-term treatment with cyclosporine in membranous nephropathy with the nephrotic syndrome

Efstathios Alexopoulos[1], Aikaterini Papagianni[1], Mzia Tsamelashvili[1], Maria Leontsini[2] and Dimitrios Memmos[1]

[1]Department of Nephrology and [2]Department of Pathology, Hippokration General Hospital, Thessaloniki, Greece

Alexopoulos E. Nephrol Dial Transplant. 2006:3127-32

Table 5. Comparative clinical data of the two groups after long-term treatment with cyclosporine

Remission	Pre + CyA ($n=26$) (Out of 31)		CyA ($n=17$) (Out of 20)	
	12 months	End of follow-up	12 months	End of follow-up
Complete	11	10	4	4
Partial	15	16	13	13
Scr (mg/dl)	1.3 ± 0.6	1.3 ± 0.4	1.1 ± 0.3	1.1 ± 0.2
Proteinuria (g/24 h)	1.1 ± 1.7	1.0 ± 1.4	1.1 ± 0.8	1.0 ± 0.7

Values are means ± SD.

- During long-term treatment relapses were more frequent in the monotherapy group (47 vs 15%, P<0.05).
- Daily CyA dose was higher in nonrelapsers in both groups.
- Relapsers had a lower trough level.

see commentary on page 841

Tacrolimus monotherapy in membranous nephropathy: A randomized controlled trial

M Praga[1], V Barrio[2], G Fernández Juárez[2] and J Luño[3], For the GRUPO ESPAÑOL DE ESTUDIO DE LA NEFROPATÍA MEMBRANOSA (Members of the Group listed at the end of the paper)

[1]Hospital 12 de Octubre, Madrid, Spain; [2]Fundación Hospital Alcorcón, Alcorcón, Madrid, Spain and [3]Hospital Gregorio Marañón, Madrid, Spain

Membranous nephropathy is a common cause of nephrotic syndrome in adults. Although some patients with membranous nephropathy achieve a spontaneous remission, renal function continues to deteriorate in others. We conducted a prospective randomized trial evaluating monotherapy with tacrolimus to achieve complete or partial remission in patients with biopsy-proven membranous nephropathy. Twenty-five patients received tacrolimus (0.05 mg/kg/day) over 12 months with a 6-month taper, whereas 23 patients were in the control group. The probability of remission in the treatment group was 58, 82, and 94% after 6, 12, and 18 months but only 10, 24, and 35%.

Membranous nephropathy (MGN) is a frequent cause of nephrotic syndrome in adults. Although the treatment of MGN remains a much-debated issue, the number of randomized controlled trials testing specific therapeutic alternatives is scarce. Immunosuppressive therapy with steroids and cytotoxics such as chlorambucil or cyclophosphamide has demonstrated a good efficacy in patients with nephrotic syndrome and normal renal function in several prospective trials.[1–3] Nevertheless, serious adverse effects of these aggressive therapeutic approaches are an important concern, considering the advanced age of the majority of MGN patients. On the other hand, a considerable percentage

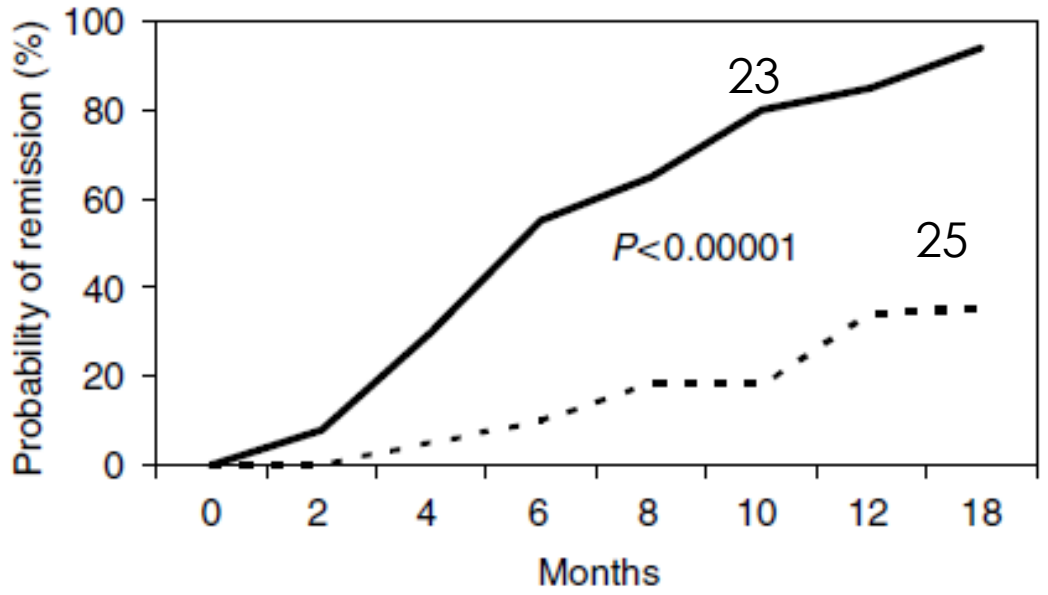


Figure 4 | Probability of remission (either CR or PR) in tacrolimus-treated group (solid line) and control group (dashed line) (log-rank test $P < 0.00001$).

The probability of remission in the treatment group was 58, 82, and 94% after 6, 12, and 18 months but only 10, 24, and 35%, respectively in the control group.

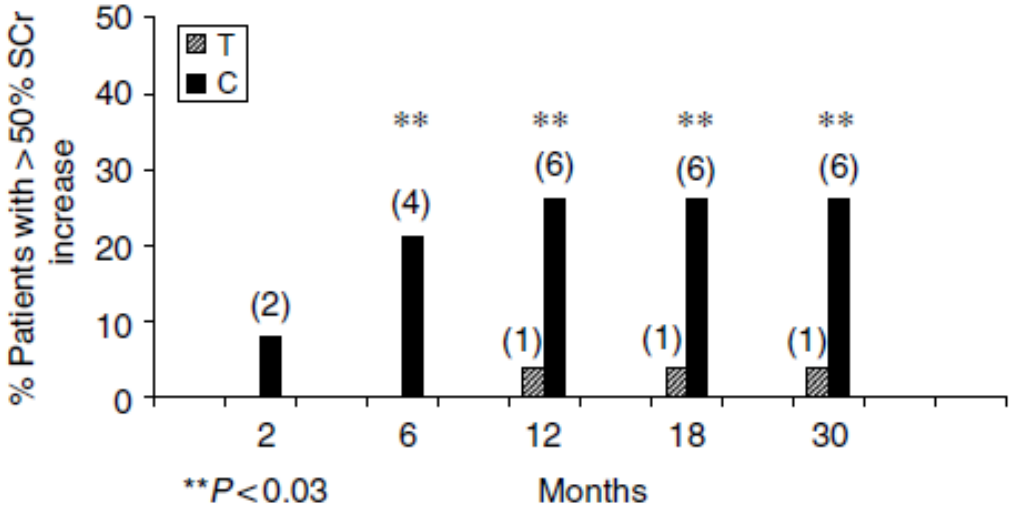


Figure 5 | Percentage of patients reaching the secondary end point (a 50% SCr increase) during the study in tacrolimus-treated group (T) and control group (C).

KDIGO

***Cyclosporine*:** 3.5–5.0 mg/kg/d given orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/kg/d, for 6 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity (Sandimmune®, Neoral®, and generic cyclosporin considered equivalent).

***Tacrolimus*:** 0.05–0.075 mg/kg/d given orally in two divided doses 12 hours apart, without prednisone, for 6–12 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity.

The highest level of evidence, IA recommended in the GN guidelines, is for the Ponticelli regimen, a 6-month cycling of an alkylating agent with steroids.

Kidney International, Vol. 48 (1995), pp. 1600–1604

A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy

CLAUDIO PONTICELLI, PIETRO ZUCCHELLI, PATRIZIA PASSERINI, BRUNO CESANA, FRANCESCO LOCATELLI, SONIA PASQUALI, MAURO SASDELLI, BRUNO REDAELLI, CLAUDIO GRASSI, CLAUDIO POZZI, DANIELA BIZZARRI, and GIOVANNI BANFI

Ponticelli C . KI.1995:1600-4

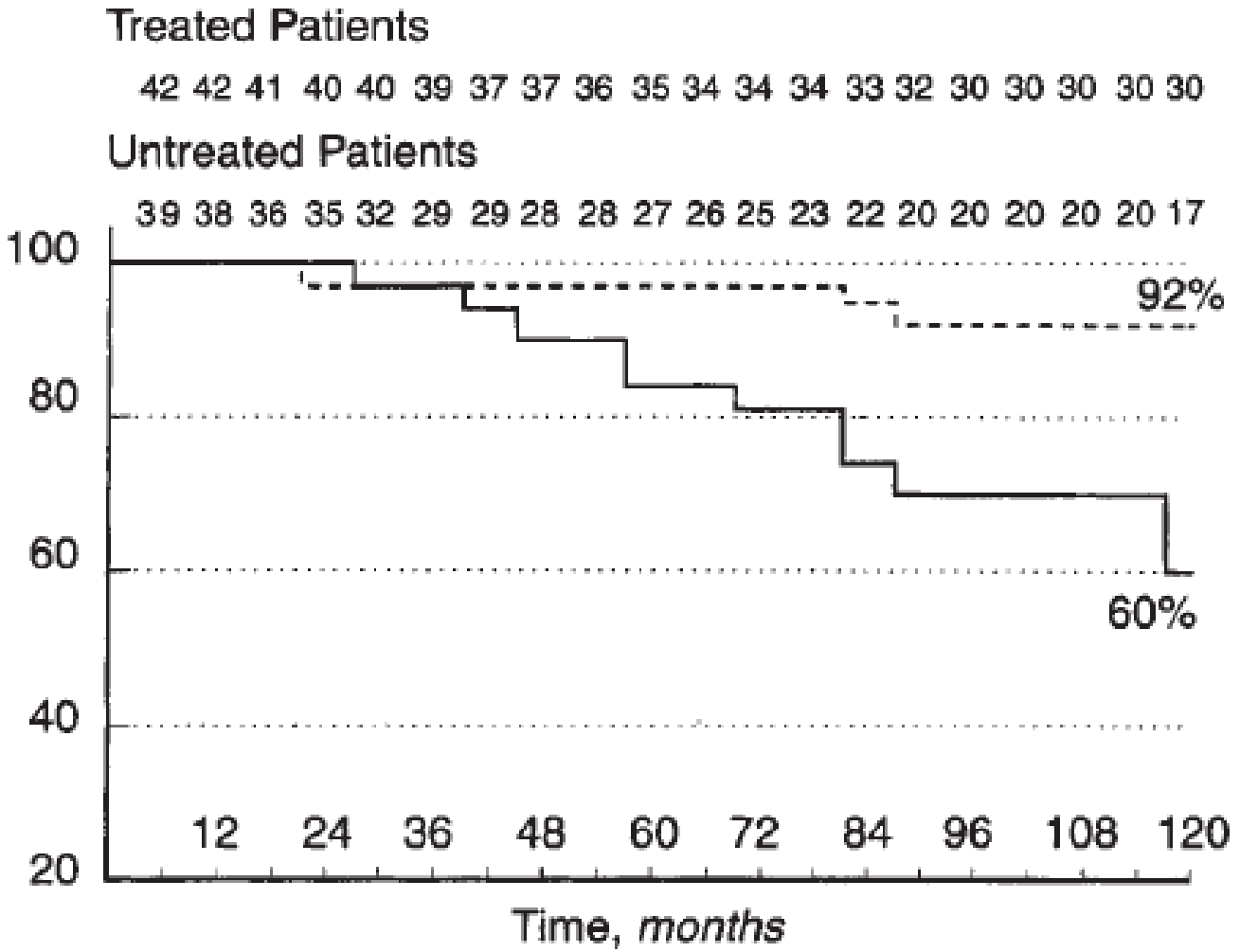


Fig. 1. *Cumulative probability of survival without dialysis in patients who received treatment (- - -) and in untreated controls (——).* The difference is significant ($P = 0.0038$).

Table 1. Clinical status at the last follow-up visit

	Treated patients	Untreated patients
Total	42	39
Complete remission	17 (5)	2
Partial remission	9 (1)	11 (1)
Nephrotic syndrome	9 (3)	6 (6)
Renal dysfunction	4	8 (3)
Dialysis	2	9
Death	1	3

In brackets are the patients lost to follow up and their clinical status at the last visit. For the definitions see **Methods.**

Ponticelli C . Kidney Int. 1995 :1600-4.

Side Effects

- 4 patients assigned to methylprednisolone and chlorambutil had to stop therapy between the 3rd and 4th month because of side-effects (two peptic ulcers, one pneumonitis, one gastric intolerance to chlorambucil).
- 2 other patients had moderate leukopenia, 2 tremors, 2 cramps and 1 anxiety. 2 patients had gastric pain during chlorambucil and 1 developed an increase in serum transaminases.
- All these side-effects reversed after treatment was completed
- In the long-term 1 patient developed obesity and 1 DM 4 years after treatment.
- No other side effects were reported in the long-term follow-up.

A Randomized, Controlled Trial of Steroids and Cyclophosphamide in Adults with Nephrotic Syndrome Caused by Idiopathic Membranous Nephropathy

Vivekanand Jha,* Anirban Ganguli,* Tarun K. Saha,* Harbir S. Kohli,* Kamal Sud,* Krishan L. Gupta,* Kusum Joshi,† and Vinay Sakhuja*

*Departments of *Nephrology and †Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Idiopathic membranous nephropathy (IMN) is the most common cause of nephrotic syndrome in adults. Universal consensus regarding the need for and the modality of therapy has not been formed because of a lack of controlled trials of sufficient size, quality, and duration. This study compared the effect of a 6-mo course of alternating prednisolone and cyclophosphamide with supportive treatment in adults with nephrotic syndrome caused by IMN on doubling of serum creatinine, development of ESRD, and quality of life in a randomized, controlled trial. Patients were followed up for 10 yr. Data were analyzed on an intention-to-treat basis. A total of 93 patients completed the study. Of the 47 patients who received the experimental protocol, 34 achieved remission (15 complete and 19 partial), compared with 16 (five complete, 11 partial) of 46 in the control group ($P < 0.0001$). The 10-yr dialysis-free survival was 89 and 65% ($P = 0.016$), and the likelihood of survival without death, dialysis, and doubling of serum creatinine were 79 and 44% ($P = 0.0006$) in the two groups. Treated patients exhibited significantly lower prevalence of edema, hypertension, hypoalbuminemia, hyperlipidemia that required therapy, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use, and better quality of life on follow-up. The incidence of infections was similar in the two groups. In conclusion, untreated IMN with nephrotic syndrome is associated with a high risk for deterioration of renal function. A 6-mo regimen of cyclophosphamide and steroids induces remissions in a high proportion, arrests progression of renal insufficiency, and improves quality of life.

J Am Soc Nephrol 18: 1899–1904, 2007. doi: 10.1681/ASN.2007020166

Month 1: i.v. methylprednisolone (1 g) daily for three doses, then oral methyprednisolone (0.5 mg/kg/d) for 27 days
Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2.0 mg/kg/d) for 30 days[a]
Month 3: Repeat Month 1
Month 4: Repeat Month 2
Month 5: Repeat Month 1
Month 6: Repeat Month 2

IMN, idiopathic membranous nephropathy.

[a]Monitor every 2 weeks for 2 months, then every month for 6 months, with serum creatinine, urinary protein excretion, serum albumin, and white blood cell count. If total leukocyte count falls to $<3500/mm^3$, then hold chlorambucil or cyclophosphamide until recovery to $>4000/mm^3$.

..Cycloph/ Steroid

– Conservative Rx

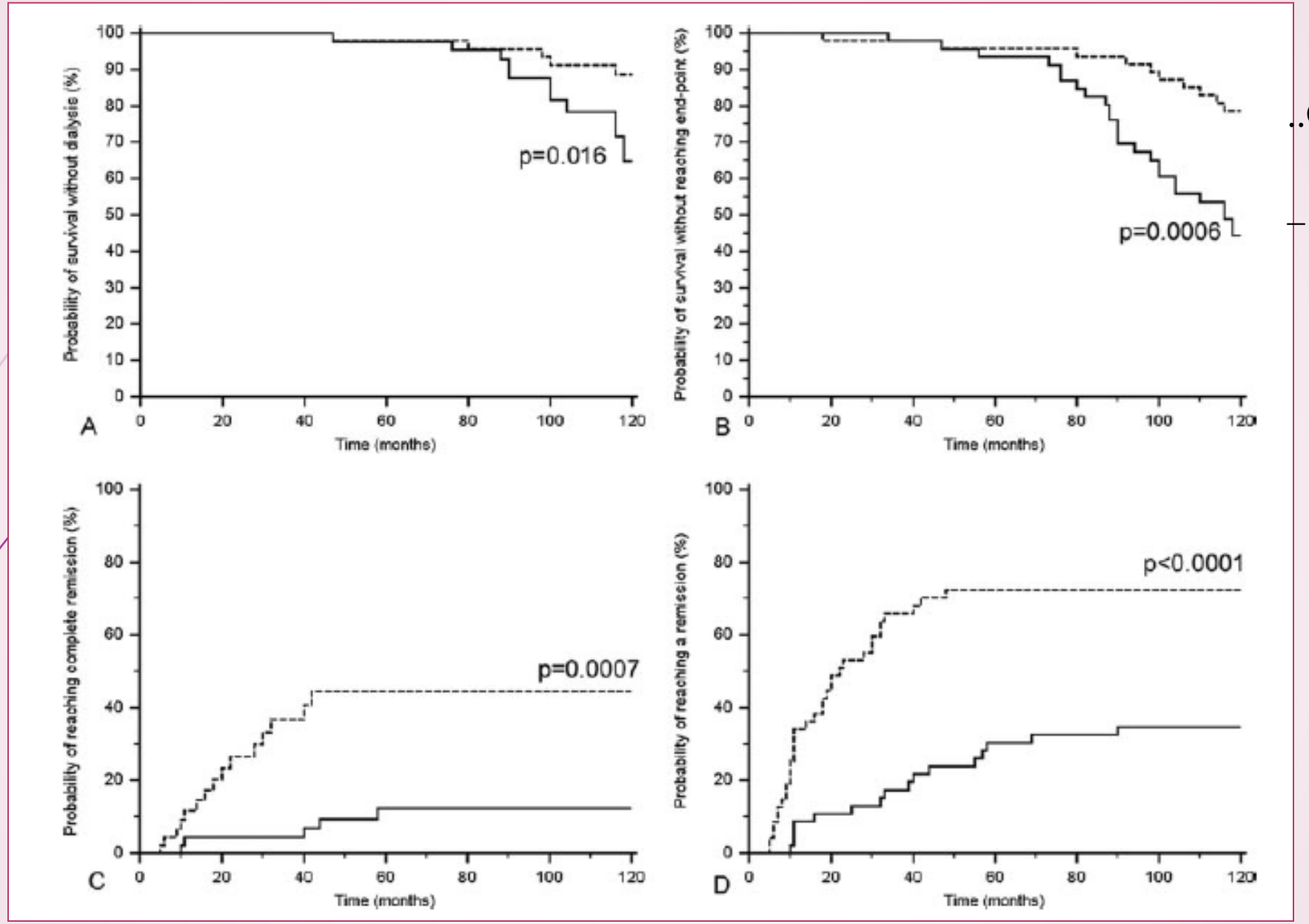


Figure 1. Kaplan-Meier plots showing probabilities of dialysis-free survival (A), survival without reaching either end point (B), complete remission (C), and complete or partial remission (D).

Complications

- Infections were the most frequent complication,
- In group 1 (conservative), 14 were noted in 11 patients, and in group 2,10 episodes were encountered in 7 patients (*P 0.35)*.
- *Thrombotic* episodes were seen in four patients in group 1 and three in group 2.
- No evidence of malignancy was seen in either of the groups during the follow-up period.

Jha V. JASN. 2007: 1899–1904

In this study, the cumulative cyclophosphamide dose of **21–46 g** (mean 37 g) over 12 months exceeded the cumulative exposure associated with the traditional cyclical cyclophosphamide dose.

van den Brand JA. CJASN. 2014:1066-73

Rituximab for idiopathic membranous nephropathy

Giuseppe Remuzzi, Carlos Chiurchiu, Mauro Abbate, Verusca Brusegan, Mario Bontempelli, Piero Ruggenenti

Treatments for idiopathic membranous nephropathy, a common cause of nephrotic syndrome, can be very toxic. In view of the pathogenic potential of B cells in this disease, we studied the effects of four weekly infusions of rituximab (375 mg/m^2)— the monoclonal antibody to B-cell antigen CD20—in eight patients who had idiopathic membranous nephropathy with persistent nephrotic syndrome. At weeks 4 and 20, urinary protein decreased from mean (SE) 8·6 g/24 h (1·4) to 3·8 (0·8) and 3·7 (0·9), respectively (p<0·0001). At week 20, albuminuria and albumin fractional clearance decreased by 70% and 65%, and serum albumin increased by 31%. CD20 B lymphocytes fell below normal ranges up to study end. The short-term risk-benefit profile of rituximab seems more favourable to that of any other immunosuppressive drug used to treat idiopathic membranous nephropathy.

Lancet 2002; **360:** 923–24

Current therapeutic approaches to idiopathic membranous nephropathy (IMN), the most common cause of nephrotic

specifically interfere with B cells would ideally represent the first step toward selective therapy. The success of such treatments would also provide evidence for the role of a B-cell-related mechanism in IMN.[4]

Therefore, we investigated the efficacy and safety profile of rituximab (Roche SpA, Monza, Italy), a monoclonal antibody against the cell surface antigen CD20 of B cells,[5] in three men and four women with IMN. Patients' average age was 52 years (range 24–75). They had creatinine clearance greater than 20 mL/min/1·73 m^2, persistent urinary protein excretion rate greater than 3·5 g/24 h for at least 6 months, and were on full-dose angiotensin-converting-enzyme (ACE) inhibitors and without remission over 29·7 (13–49) months from renal biopsy. Patients gave written informed consent to study participation according to the declaration of Helsinki. Seven patients were on diuretics or statins (or both), two were on non-dihydropyridine calcium-channel blockers, three were on aspirin, and one was on oral anticoagulant therapy.

We gave the patients intravenous infusions of rituximab

Rituximab: depletes B cells by Ab-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis

	Week									
	–24	0	1	2	3	4	8	12	16	20
Patient										
1	16·8	16·0	13·6	8·4	7·6	9·5	9·1	8·9	8·7	5·8
2	7·2	7·0	4·5	3·3	3·9	2·9	2·6	3·1	2·7	3·3
3	4·2	4·8	4·8	1·8	2·5	1·4	2·7	1·0	0·6	0·4
4	5·6	5·6	4·4	3·1	3·5	3·5	4·8	5·6	5·7	5·6
5	4·5	5·7	2·9	2·8	2·7	2·8	1·7	2·3	1·9	1·7
6	8·5	9·1	5·8	4·7	2·3	3·2	5·9	1·5	1·4	1·0
7	14·0	14·1	11·0	8·2	8·3	3·8	4·1	9·4	7·8	8·0
8	6·5	6·7	3·0	2·5	2·9	3·0	2·0	3·1	3·5	3·5
Mean (SE)	8·4 (1·6)	8·6 (1·5)	6·3* (1·4)	4·4* (0·9)	4·2* (0·9)	3·8* (0·9)	4·1* (0·9)	4·3* (1·1)	4·0* (1·1)	3·7* (0·9)

*p<0·0001 versus week –24 and week 0.

Table 1: **Time course of 24 h urinary protein excretion rate (g/24 h) in individual patients from 24 weeks before study entry (week 0) up to study end (week 20)**

-375 mg/m^2 every 4 weeks in 8 patients with refractory primary MN and nephrotic syndrome.

-Mean urinary protein decreased from 8.6 g/day at baseline to 3.7 g/day at 20 weeks' follow-up

-Two patients achieved full remission, and 3 achieved partial remission.

-Reduction in proteinuria >50% was seen in 5 patients.

Remuzzi G. Lancet. 2002 ;360:923-4.

Rituximab treatment of idiopathic membranous nephropathy

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Idiopathic membranous nephropathy is a common cause of nephrotic syndrome whose pathogenesis may involve B-cell functions. Rituximab is a monoclonal antibody that binds to the CD20 antigen on B cells thereby deleting them. We

Idiopathic membranous nephropathy (IMN) is the most common cause of nephrotic syndrome in Caucasian adults and the second or third cause of a primary glomerulopathy leading to end-stage renal disease.[1] Although, in most

Fervenza FC KI 2008: 117–125

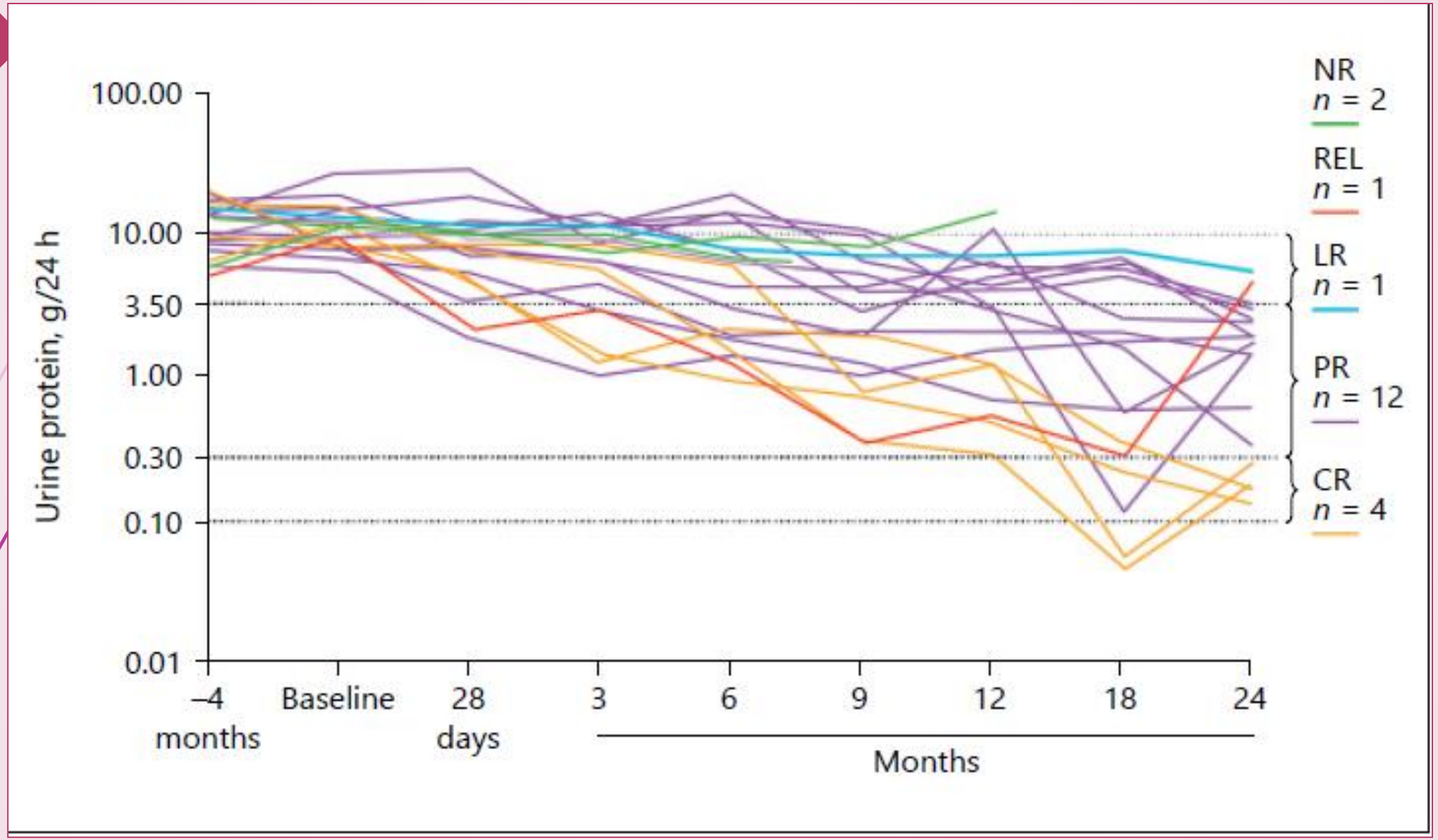
Table 2 | Time course of urinary protein excretion (g per 24 h) in individual patients with IMN from entry into the study (baseline) to end of study (month 12)

Patient no.	Month −6	Baseline	Month 1	Month 3	Month 6	Month 9	Month 12	Baseline to month 12[a]
1[b]	10.6	9.1	7.4	5.9	18.8	7.4	7.7	1.4
2[b]	12.9	8.4	8.9	6.3	3.9	2.2	0.6	7.8
3	7.9	8.5	6.1	1.2	0.6	0.4	0.2	8.3
4[b]	16.4	20.1	16.5	21.8	17.9	15.4	20.2	−0.14
5	8.6	10.8	5.5	1.7	1.1	0.8	0.2	10.5
6	13.3	23.5	31.3	5.0	—	—	—	—
7[b]	10.4	16.6	7.5	14.8	17.2	17.3	19.9	−3.3
8	4.6	8.8	3.6	2.2	0.8	0.7	1.0	7.8
9[b]	7.7	10.1	8.9	7.5	4.8	8.1	0.7	9.4
10[b]	4.8	6.1	3.9	5.7	6.0	0.6	0.3	5.8
11	7.9	15.8	16.5	3.8	2.1	3.8	0.9	14.9
12[b]	12.4	7.8	3.8	1.8	4.9	3.5	2.6	5.2
13[b]	8.9	14.7	14.0	22.4	16.9	12.5	6.0	8.7
14[b]	12.3	23.4	16.4	22.0	26.5	17.4	14.1	9.4
15[b]	8.8	11.8	9.2	15.2	8.9	11.1	9.8	2.0
Mean	9.8	13.0	10.6	9.8	9.3	7.2	6.0	6.2
s.d.	3.1	5.7	7.3	7.9	8.4	6.5	7.3	4.8
Median	8.9	10.8	8.9	5.9	5.5	5.6	1.8	7.8

IMN, idiopathic membranous nephropathy.
[a]Paired *t*-test $P=0.0003$ for 12-month change.
[b]Patients who underwent retreatment with rituximab.

- 14 patients treated with 1 g rituximab at time 0 and again after 15 days, with re-treatment at 6 months in those with no response.
- At 1-year follow-up, 2 and 6 patients achieved complete and partial remission,
- No relationship was found between the response and number of B cells in the blood, CD20 cells in the kidney biopsy, degree of tubulointerstitial fibrosis, starting proteinuria or creatinine values.

Fervenza FC KI 2008: 117–125



Fervenza FC KI 2008: 117–125

CLINICAL RESEARCH www.jasn.org

Rituximab in Idiopathic Membranous Nephropathy

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ABSTRACT

Selective depletion of B cells with the mAb rituximab may benefit the autoimmune glomerular disease idiopathic membranous nephropathy (IMN). Here, we describe our experience treating 100 consecutive IMN patients with persistent nephrotic syndrome with rituximab. We defined complete remission as persistent proteinuria <0.3 g/24 h and partial remission as persistent proteinuria <3 g/24 h, each also having >50% reduction in proteinuria from baseline. During a median follow-up of 29 months after

Rugenneti JASN 2012:1416–1425

Table 1. Baseline characteristics of patients in the study group as a whole (overall) and in patients with complete, partial, or no remission or who received rituximab as first- or second-line therapy, considered separately

Characteristic	Overall (*n*=100)	Complete Remission (*n*=27)	Partial Remission (*n*=38)	No Remission (*n*=35)	First-Line Therapy (*n*=68)	Second-Line Therapy (*n*=32)
Age (yr)	51.5±5.9	48.9±16.5	51.4±15.6	53.7±15.9	55.0±16.4	44.1±12.0[a]
Male sex, *n* (%)	72 (72)	13 (48.1)[b]	28 (73.7)	31 (87.5)	46 (67.6)	26 (81.3)
Clinical parameters						
body weight (kg)	76.2±13.6	70.5±15.6	78.2±12.2	78.3±12.7	76.1±12.1	76.5±16.5
systolic BP (mmHg)	130 (122–144)	129 (119.5–139)	132.5 (123–150)	135.5 (127–145)	130 (123–146)	130 (121–140)
diastolic BP (mmHg)	82 (74–90)	80 (73.5–86.5)	84 (76–90)	83 (75–90)	84 (72.5–90)	81 (76–86)
Laboratory parameters						
serum creatinine (mg/dl)	1.2 (0.97–1.7)	1.01 (0.84–1.13)[b,c]	1.2 (1–1.6)	1.6 (1.1–2.4)	1.2 (0.95–1.8)	1.1 (0.97–1.6)
serum albumin (g/dl)	2.2±0.6	2.5±0.6[b]	2.2±0.7	2.0±0.5	2.2±0.6	2.2±0.6
total cholesterol (mg/dl)	272 (214–318)	232.5 (209–295)	277 (206–318)	288 (225–351)	257 (214–320)	288 (221–314.5)
HDL cholesterol (mg/dl)	52 (42–65)	63 (51–73)[b,c]	49 (42–61)	48 (39–58)	54 (42–66)	47.5 (40–60.5)
triglycerides (mg/dl)	158 (110–228)	110 (80–147)[b,c]	146 (130–205)[b]	227 (142–300)	142 (100–223)	191 (134.5–256.5)
proteinuria (g/24 h)	9.1 (5.8–12.8)	5.8 (4.3–9.6)[b]	8.2 (5.8–11.2)[b]	12.9 (9.4–18.5)	9.3 (5.8–12.7)	9 (6.4–13.3)
duration of persistent proteinuria (mo)	25.5 (11.7–67.7)	23.4 (12.3–63.6)	20.6 (11.9–66.3)	32.5 (11–76.4)	16.7 (9.2–31.4)	65.4 (35–80.5)[a]

Complete or partial remission (Similar Proportion)

47 of 68 (69.1%)

18 of 32 (56.25%)

Table 2. Patients with at least one serious adverse event in the study group as a whole (overall) and according to disease outcome (complete, partial, or no remission)

Serious Adverse Event	Overall	Complete Remission	Partial Remission	No Remission
Fatal	4	0	1	3
cardiovascular	3	0	1	2
stroke	1	0	1	0
acute MI	2	0	0	2
cancer[a]	1	0	0	1
Nonfatal	7	1	2	4
cardiovascular	5	1	1	3
stroke	2	0	0	2
acute MI[b]	1	0	1	0
TIA	2	1	0	1
cancer[c]	2	0	1	1
Total	11	1	3	7

The incidence of events in participants with complete remission was lower than in those with partial or no remission (P=0.037, Cochran–Armitage test for trend). MI, myocardial infarction; TIA, transitory ischemic attack.

[a]Lung cancer.

[b]Event during a relapse of nephrotic syndrome.

[c]Breast and prostate cancer.

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ORIGINAL ARTICLE

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

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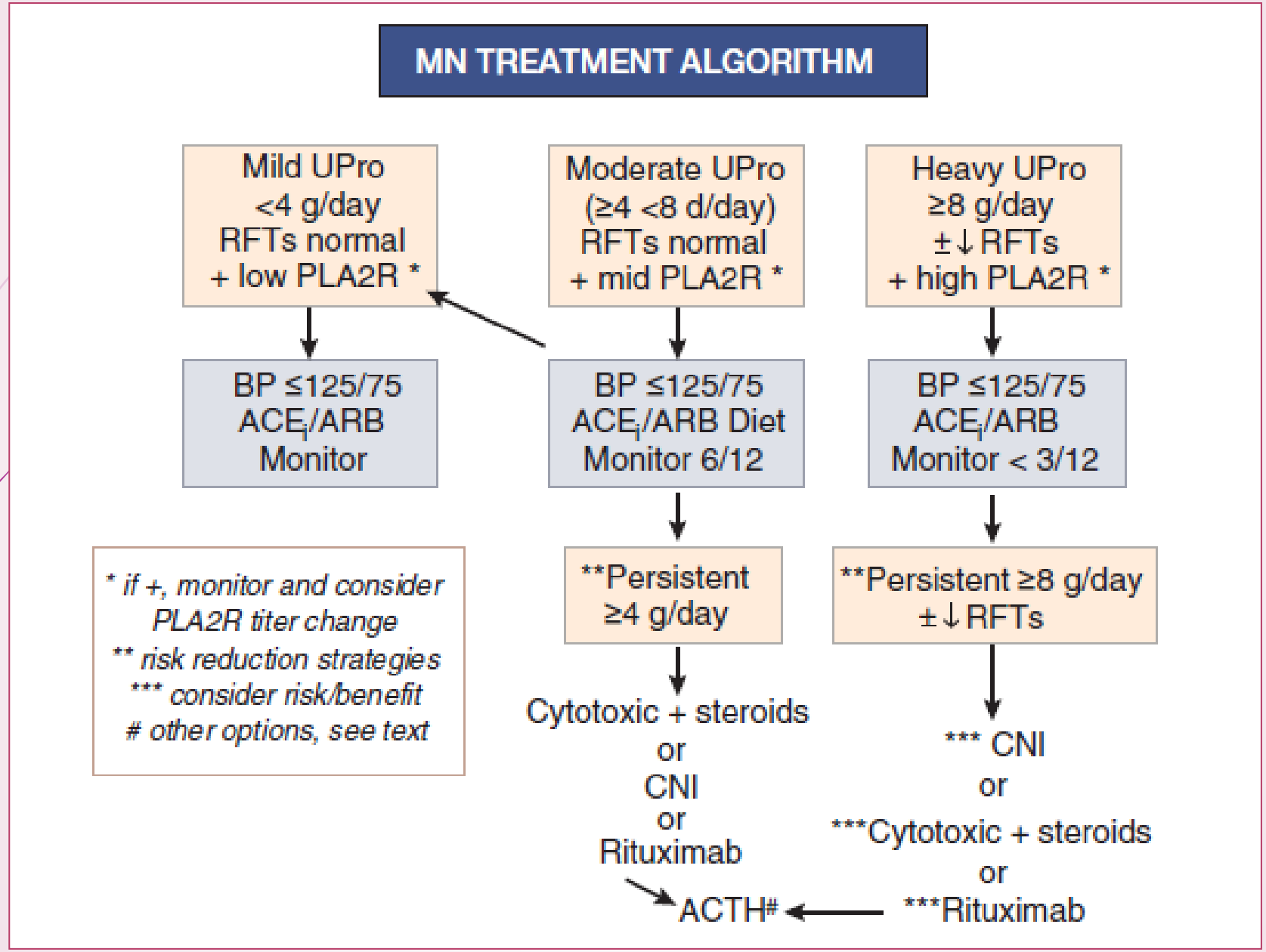
Table 2. Treatment details of individual patients

No.	Age (years)	Gender[a]	SCr 1 (mg/dL)	SAlb 1 (g/dL)	Urinary protein 1 (g/day)	Prior IS before RTX	Serum anti-PLA2R antibody before RTX therapy	Follow-up after RTX therapy (months)	SCr 2 (mg/dL)	SAlb 2 (g/dL)	Urinary protein 2 (g/day)	Status at last follow-up
1	19	M	0.8	1.8	12.2	MPR	ND	20.5	0.6	4.3	0.2	CR
2	32	M	0.8	3.1	8.8	MPR	POS	12.8	0.8	5	0.3	CR
3	43	F	0.6	2.8	7.1	MPR/TAC	POS	11.1	0.5	4.7	0.4	CR
4	18	M	0.8	1.6	6	TAC	NEG	11.2	0.7	3.8	0.2	CR
5	20	M	1.5	2.5	6.5	MPR/TAC	POS	22	1.4	5	2.2	PR
6	32	M	0.7	2.4	6	MPR	ND	23.9	0.8	4.8	0.8	PR
7	15	F	0.6	2.1	3.6	MPR	NEG	18.6	0.6	3.8	1.8	PR–relapsed during follow-up, responded to TAC
8	21	F	0.7	2.6	3.7	MPR/MMF/TAC	POS	18	0.6	3.6	1.2	PR
9	51	M	0.8	3.1	3.4	MPR/TAC/MMF	ND	16.5	0.8	4.7	1.3	PR
10	62	F	0.5	2.6	6.2	MPR	NEG	13.1	0.5	4.2	1.8	PR
11	37	F	0.8	3	3.4	TAC/MMF	ND	17.4	0.7	4.5	1.2	PR
12	34	M	0.8	2.4	6.2	MPR/TAC	POS	12.6	0.8	4.2	1.0	PR
13	40	F	1.5	3.1	3.6	MPR/TAC	POS	10	1.5	4.1	1.5	PR
14	40	M	0.9	1.6	4.7	TAC	ND	10.8	3.4	3.8	4.5	NR
15	46	M	1	2.8	7	MPR/TAC	POS	18.8	3.3	2.9	10.0	NR
16	33	M	1.3	2.4	5	MPR/TAC	NEG	14.3	2	3.6	11.0	NR
17	46	M	1.1	2.9	9.6	MPR/TAC	POS	12.2	1.2	1.7	15.4	NR
18	22	F	0.7	2.6	6.3	MPR/TAC/MMF	POS	13.8	0.5	2.2	6.0	NR
19	27	M	1	1.8	8	MPR	ND	12.4	5	2	6.3	NR
20	24	M	1	2.5	7.1	MPR/TAC	NEG	11.7	1.2	3.9	7.7	NR
21	38	M	1.4	2.9	6.4	TAC/MMF	POS	10.3	2.9	2.9	7.3	NR

Ongoimg Clinical Trials

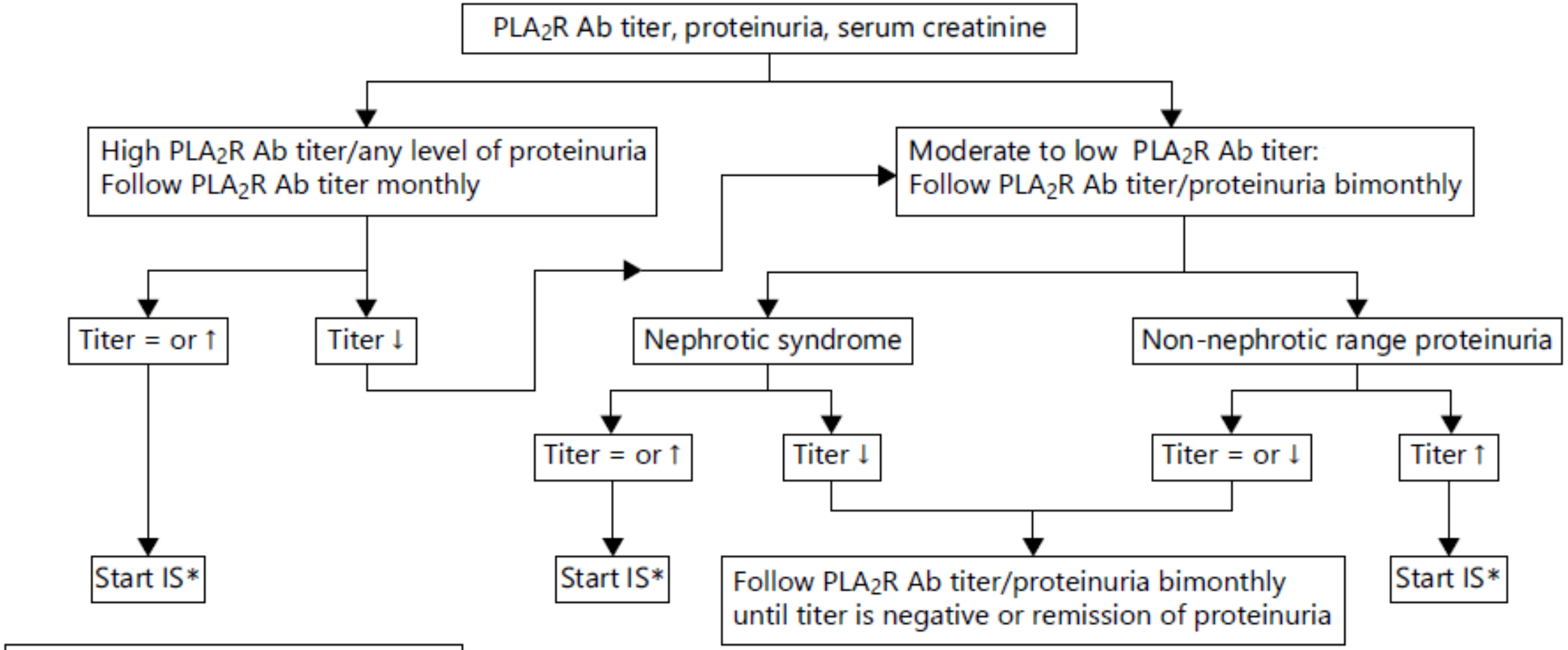
- The MEmbranous Nephropathy Trial Of Rituximab (MENTOR) study (NCT01180036) is an open-label, randomized controlled trial designed to compare efficacy and safety of rituximab (1 g IV on day 1 and 15 followed by re-treatment at 6 months) versus cyclosporine (3.5–5 mg/kg/day for 12 months) in inducing and maintaining remission in patients with primary MN.
- The STARMEN trial (NCT01955187) will evaluate tacrolimus monotherapy for 9 months (initial dose of 0.05 mg/kg/day, adjusted to achieve blood trough levels of 5–7 ng/mL for 6 months, with a single dose of rituximab 1 g IV at day 180 before the beginning of tacrolimus dose tapering) in terms of rates of remission, relapse rate, maintenance of renal function, and adverse effects during a 2-year follow-up



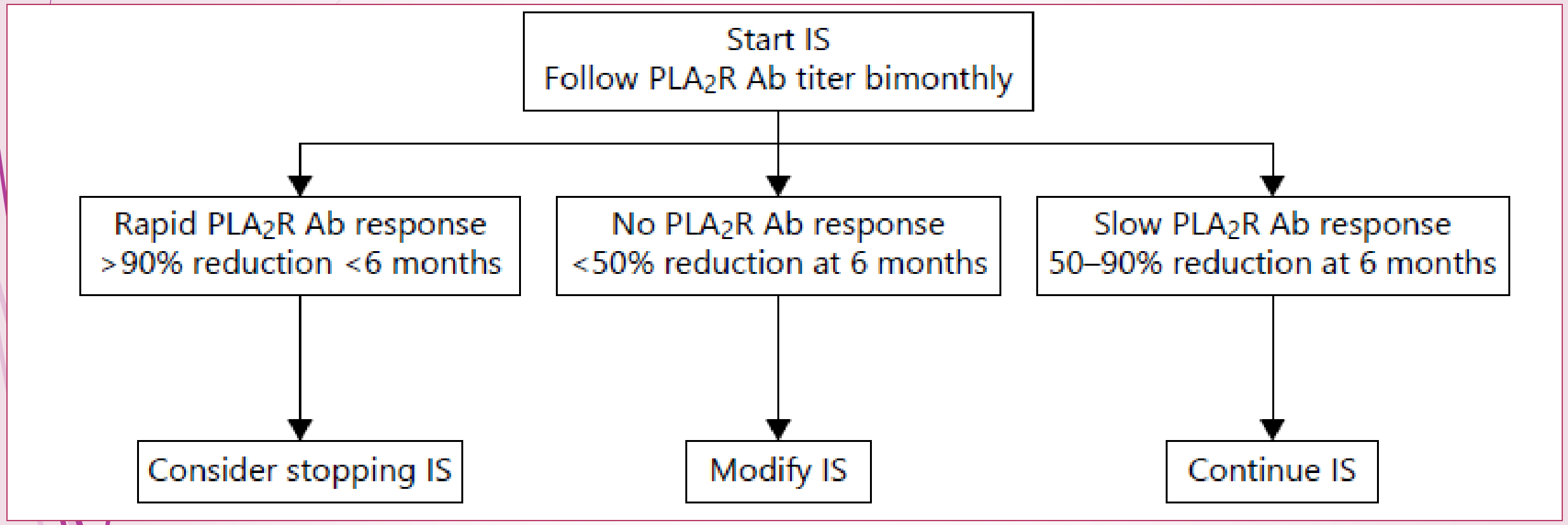
Catran DC. KI. (2017) 91, 566–574

- There is considerable evidence showing that anti- PLA 2 R antibodies correlate with disease activity, provide prognostic information about severity of disease, and can serve as a useful biomarker for assessing treatment efficacy.

Glassock RJ: CJASN 2014:1341–1343



*Unless:
- SCreat >3.5 mg/dL (>309 µmol/L)
- eGFR <30 mL/min/1.73 m^2
- Kidney size <8 cm
- Concomitant severe infections


Start IS
Follow PLA2R Ab titer bimonthly
Rapid PLA2R Ab response
>90% reduction <6 months
No PLA2R Ab response
<50% reduction at 6 months
Slow PLA2R Ab response
50–90% reduction at 6 months
Consider stopping IS
Modify IS
Continue IS

When to Stop treatment (KDIGO GN 2012)

- Serum creatinine >300 mmol/L level (or estimated GFR <30)

  and

- An ultrasound showing small and echogenic kidneys indicate irreversible kidney damage and insufficient parenchyma to warrant the risks of therapy.
- A marker of immunologic inactivity such as a PLA2R-positive patient becoming negative would further support the argument for not starting (or stopping) IS therapy.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