

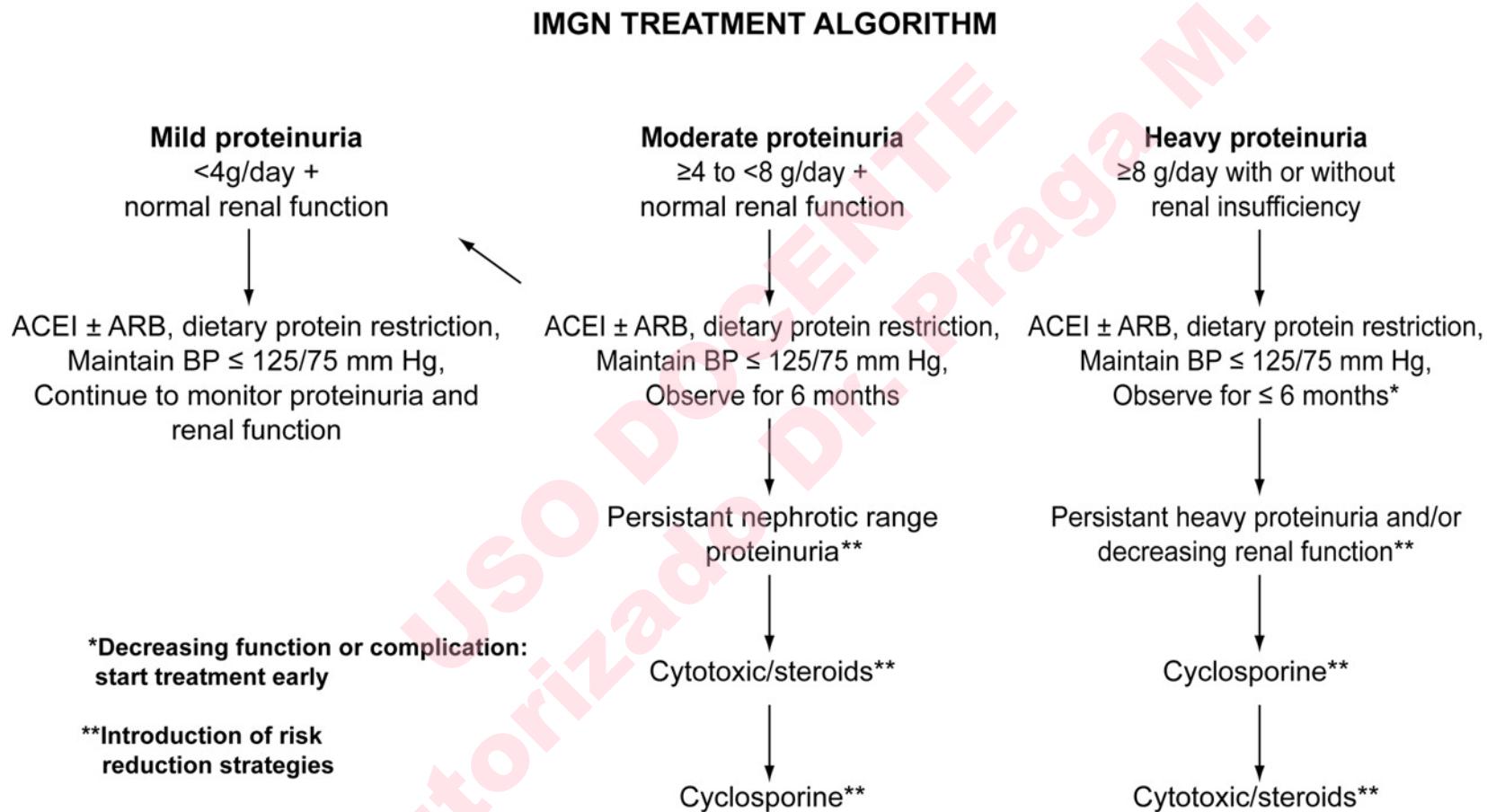
TRATAMIENTO DE LA NEFROPATÍA MEMBRANOSA

Montevideo, Uruguay
14-15 Septiembre 2015

Rule Out Secondary Membranous Nephropathy (MN)

- MN associated with Tumors, Infections or Systemic diseases.
- Drug-induced MN (Penicillamine, Gold salts, NSAIDs, Etarnecept, Infliximab, Adalimumab)
- Positivity of Anti-PLA2R
- Histopathological findings suggestive of Secondary MN:
 - Mesangial and/or subendothelial deposits in addition to subepithelial deposits
 - Cellular proliferation
 - C1q staining on IF
 - Strong or predominant deposits of IgG1, IgG2 or IgG3, instead of IgG 4

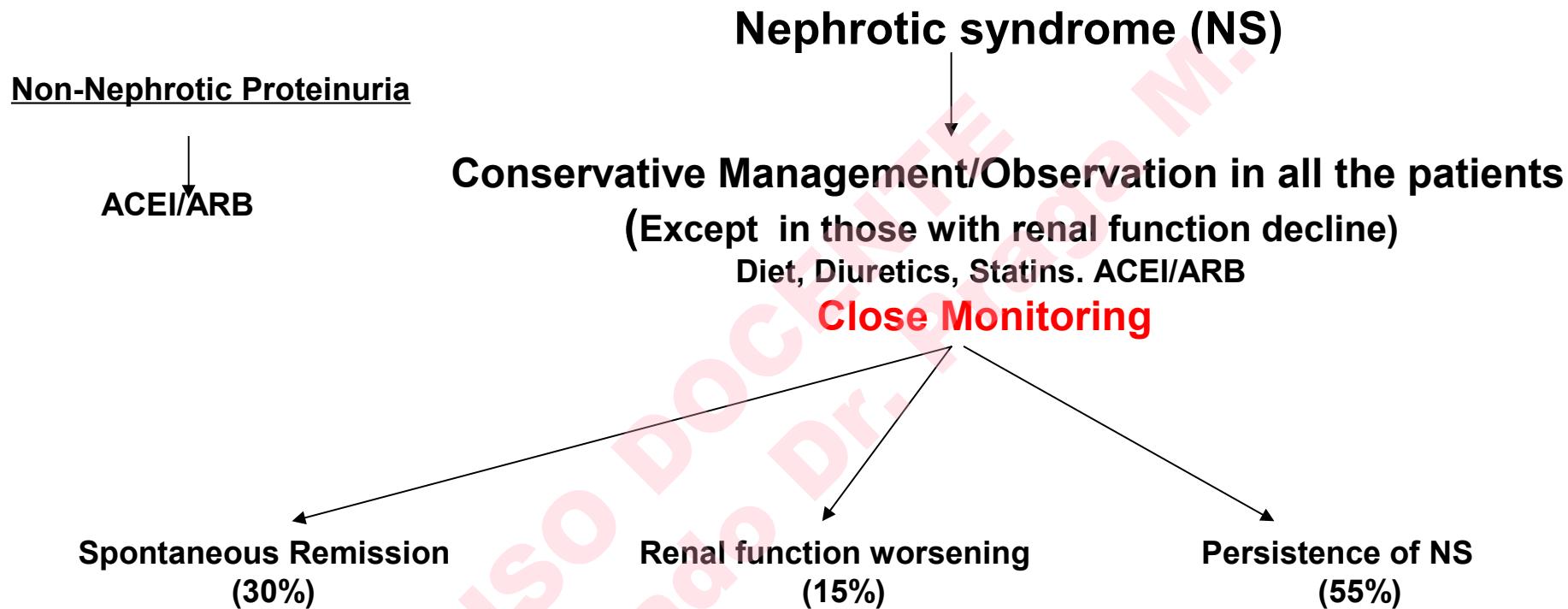
A treatment algorithm that combines the predictive factors and best evidence for conservative and then immunosuppressive treatment.



Daniel Cattran JASN 2005;16:1188-1194

JASN

Membranous Nephropathy. Therapeutic Strategy



Membranous Nephropathy

Therapeutic Strategy

Spontaneous Remission of Nephrotic Syndrome in Idiopathic Membranous Nephropathy

Natalia Polanco,* Elena Gutiérrez,* Adelardo Covarsí,[†] Francisco Ariza,[‡] Agustín Carreño,[§]
Ana Vigil,^{||} José Baltar,[¶] Gema Fernández-Fresnedo,^{**} Carmen Martín,^{††} Salvador Pons,[#]
Dolores Lorenzo,^{§§} Carmen Bernis,^{||} Pilar Arrizabalaga,^{¶¶} Gema Fernández-Juárez,^{***}
Vicente Barrio,^{***} Milagros Sierra,^{†††} Ines Castellanos,[†] Mario Espinosa,[‡] Francisco Rivera,[§]
Aniana Oliet,[¶] Francisco Fernández-Vega,[¶] and Manuel Praga* for the Grupo de Estudio de
las Enfermedades Glomerulares de la Sociedad Española de Nefrología

328 PATIENTS without Immunosuppressive treatment

Spontaneous Remission in 104 (32 %)

SPONTANEOUS REMISSION OF NEPHROTIC SYNDROME IN IDIOPATHIC MEMBRANOUS NEPHROPATHY, JASN 2010
 Polanco et al, JASN 2010

Table 3. Results of univariate and multivariate analyses of independent prognostic factors for the appearance of SR

Factor	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio for SR (95% CI)	P Value	Hazard Ratio for SR (95% CI)	P Value
Female gender	1.8 (1.10 to 3)	0.008	1.45 (0.68 to 3.10)	0.33
Baseline serum creatinine (mg/dl)	0.35 (0.18 to 0.66)	<0.001	0.40 (0.19 to 0.85)	0.018
Baseline proteinuria (g/24 h)	0.92 (0.86 to 0.98)	<0.003	0.85 (0.77 to 0.94)	<0.002
Proteinuria decrease >50% in the first year of follow-up	7.08 (3.59 to 13.9)	<0.0001	12.6 (5.2 to 30.5)	<0.0001
ACEI/ARB treatment	2 (1.1 to 3.5)	0.009	2.36 (1.09 to 5.12)	0.029

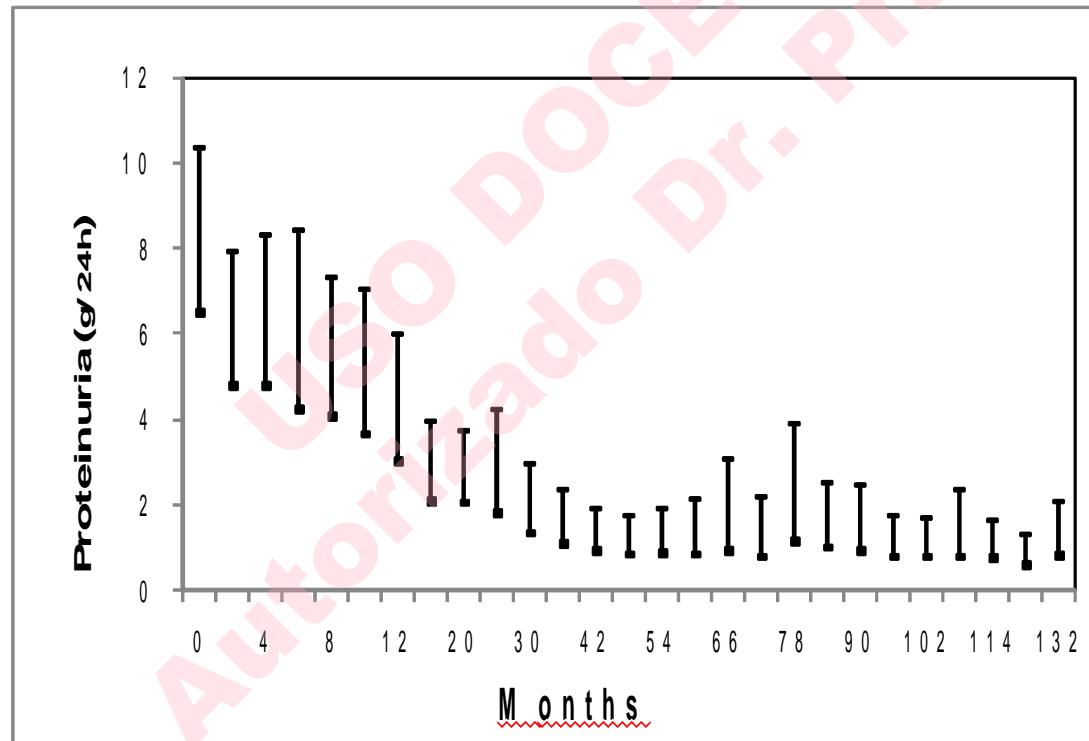
Baseline Proteinuria (g/24h)	Spontaneous remissions No. (%)	Time to remission* (months)
<4 (n=64)	33 (51.5)	17.9±16
4-8 (n=169)	72 (42.6)	14.6±13.4
8-12 (n=91)	24 (26.3)	13.6±12.5
>12 (n=51)	11 (21.5)	14±10.7

SPONTANEOUS REMISSION OF NEPHROTIC SYNDROME IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

Polanco N et al, JASN 2010

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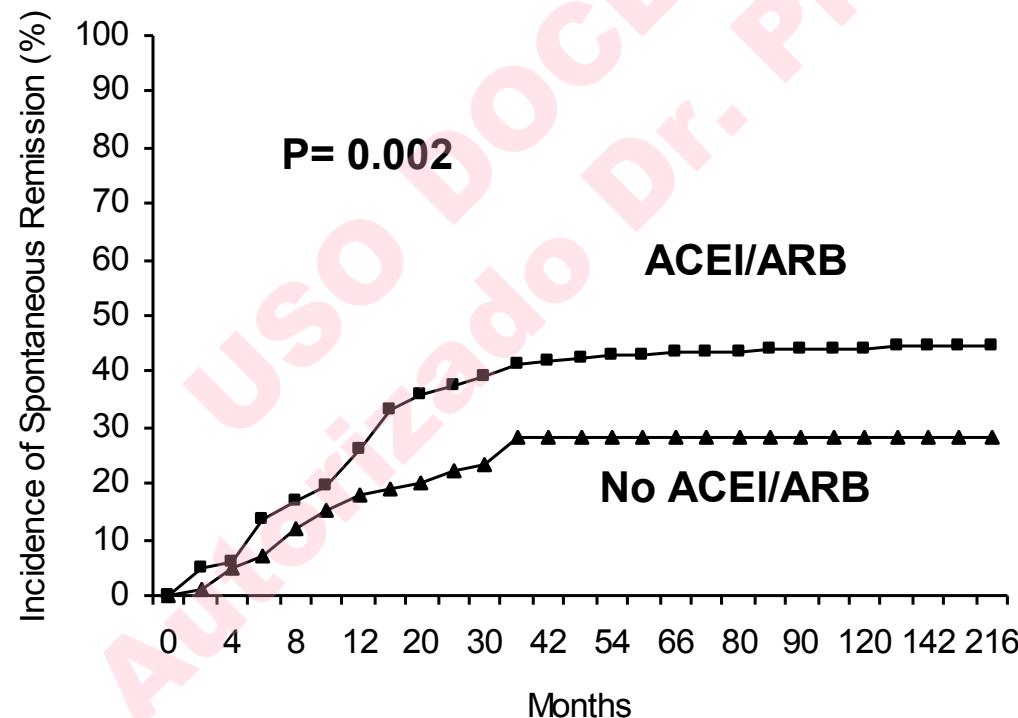
Evolution of Proteinuria in Patients with Spontaneous Remission

SPONTANEOUS REMISSION OF NEPHROTIC SYNDROME IN IDIOPATHIC MEMBRANOUS NEPHROPATHY

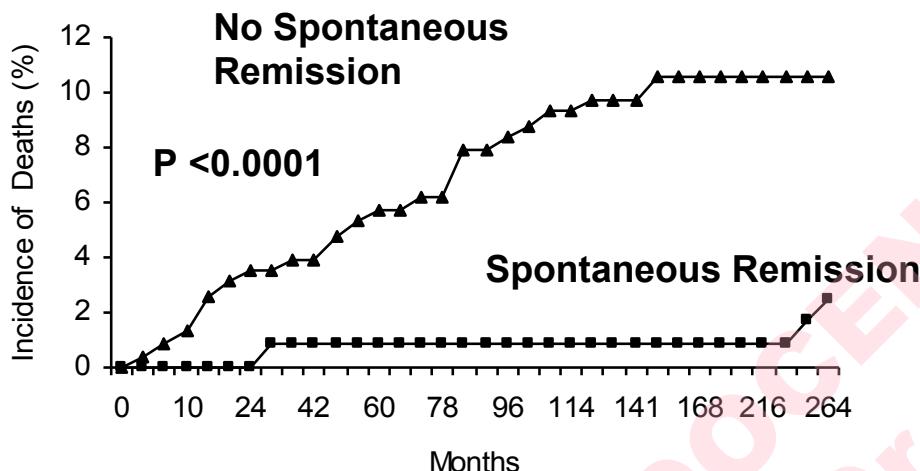
Polanco N et al, JASN 2010

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ACEI/ARB treatment	2 (1.1 to 3.5)	0.009	2.36 (1.09 to 5.12)	0.029

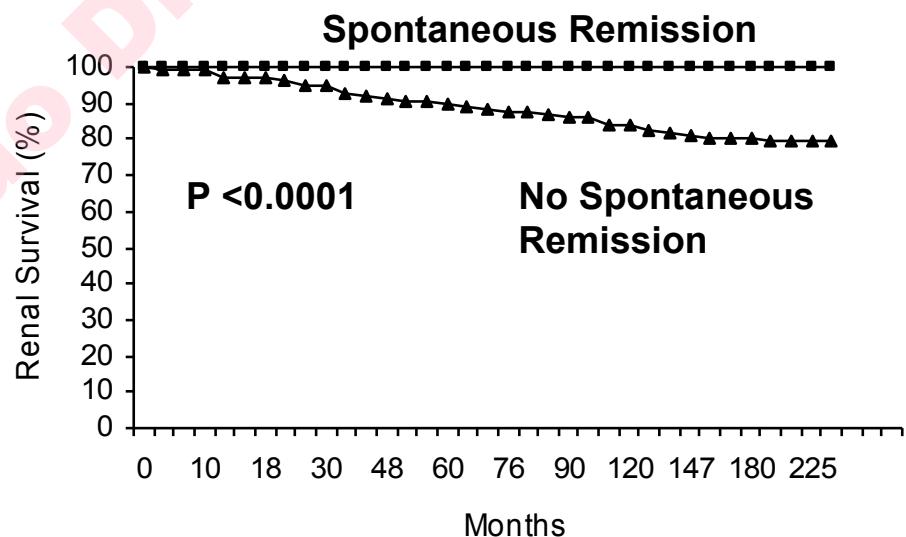


Death



NS Relapse: 5.7%

Renal Survival

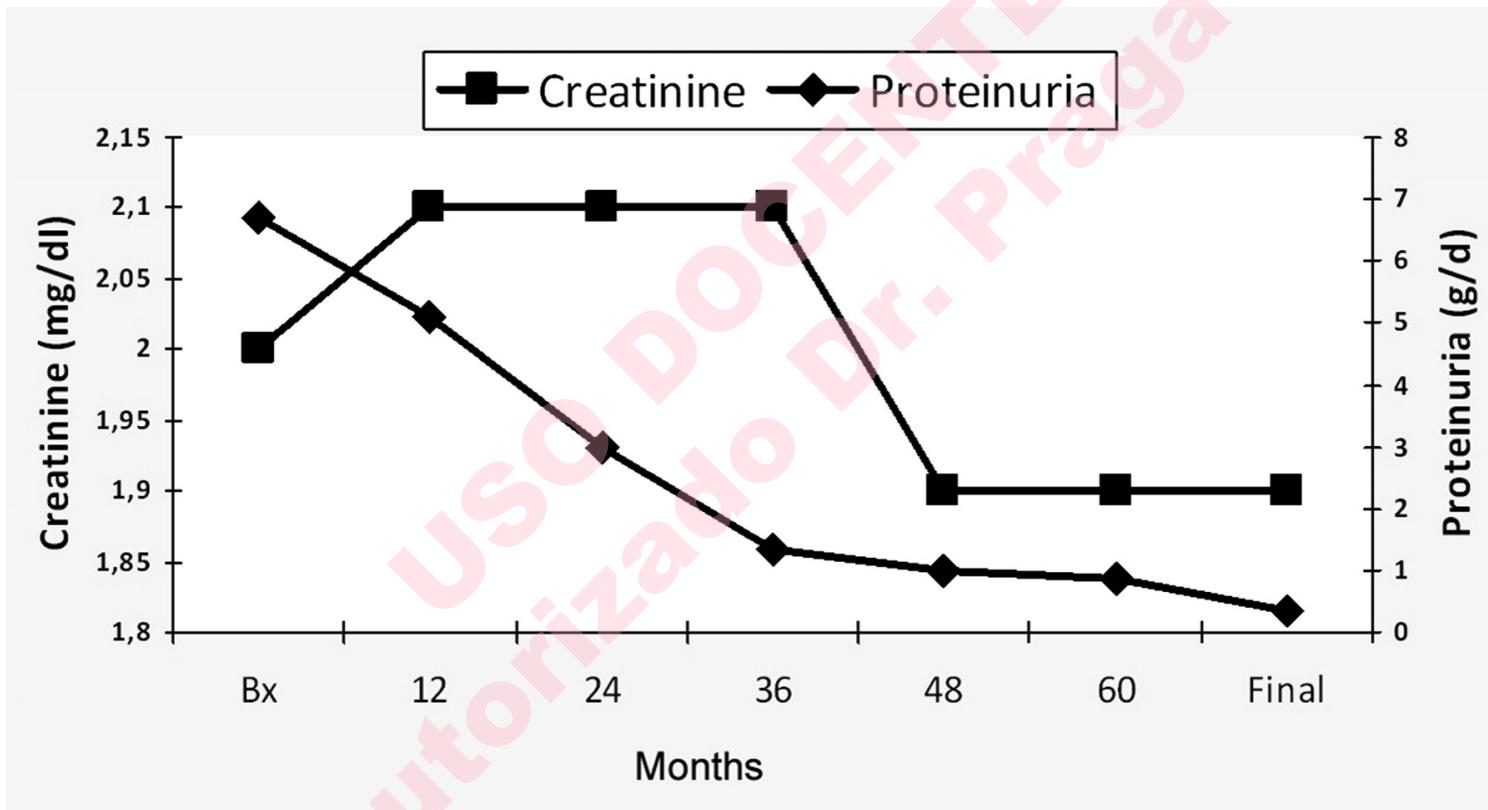


SPONTANEOUS REMISSION
WITHOUT IMMUNOSUPPRESSIVE
TREATMENT IN IDIOPATHIC MEMBRANOUS
NEPHROPATHY
(GLOSEN).

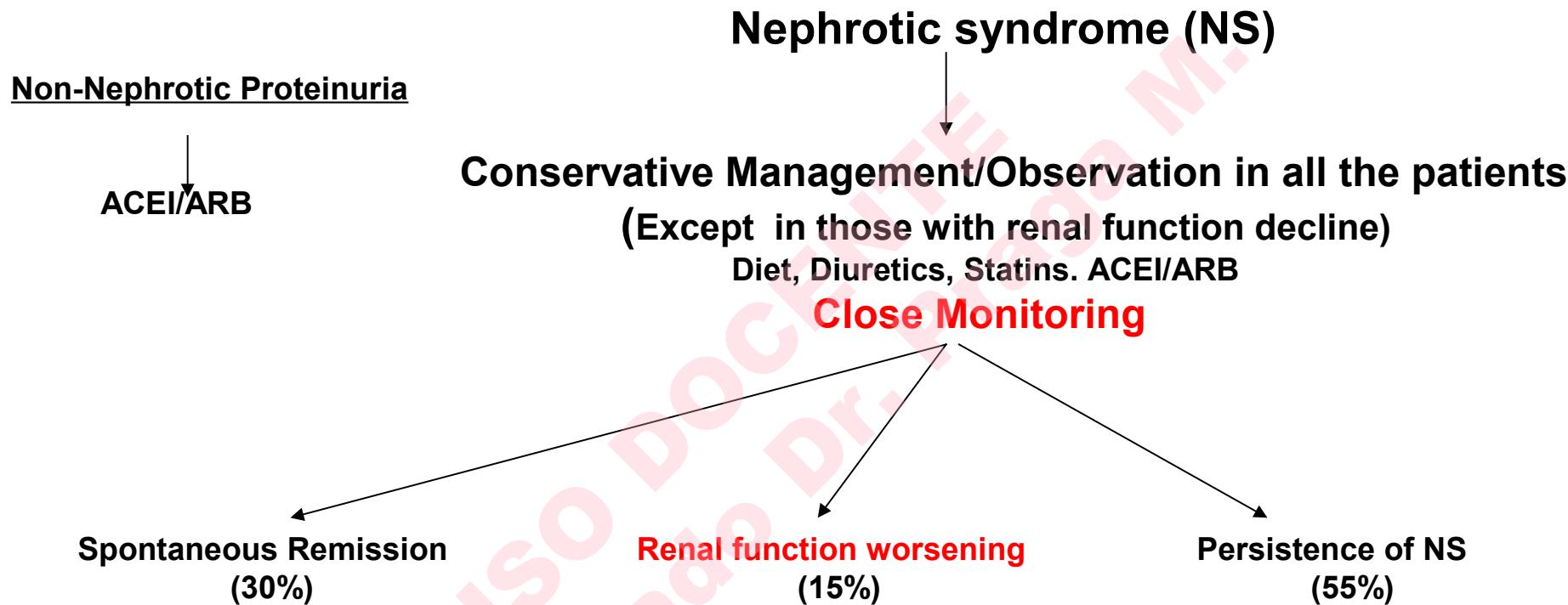
Spontaneous Remission of nephrotic syndrome in membranous nephropathy with chronic renal impairment

Polanco et al; GLOSEN. NDT 2011

Evolution of mean Scr and proteinuria.

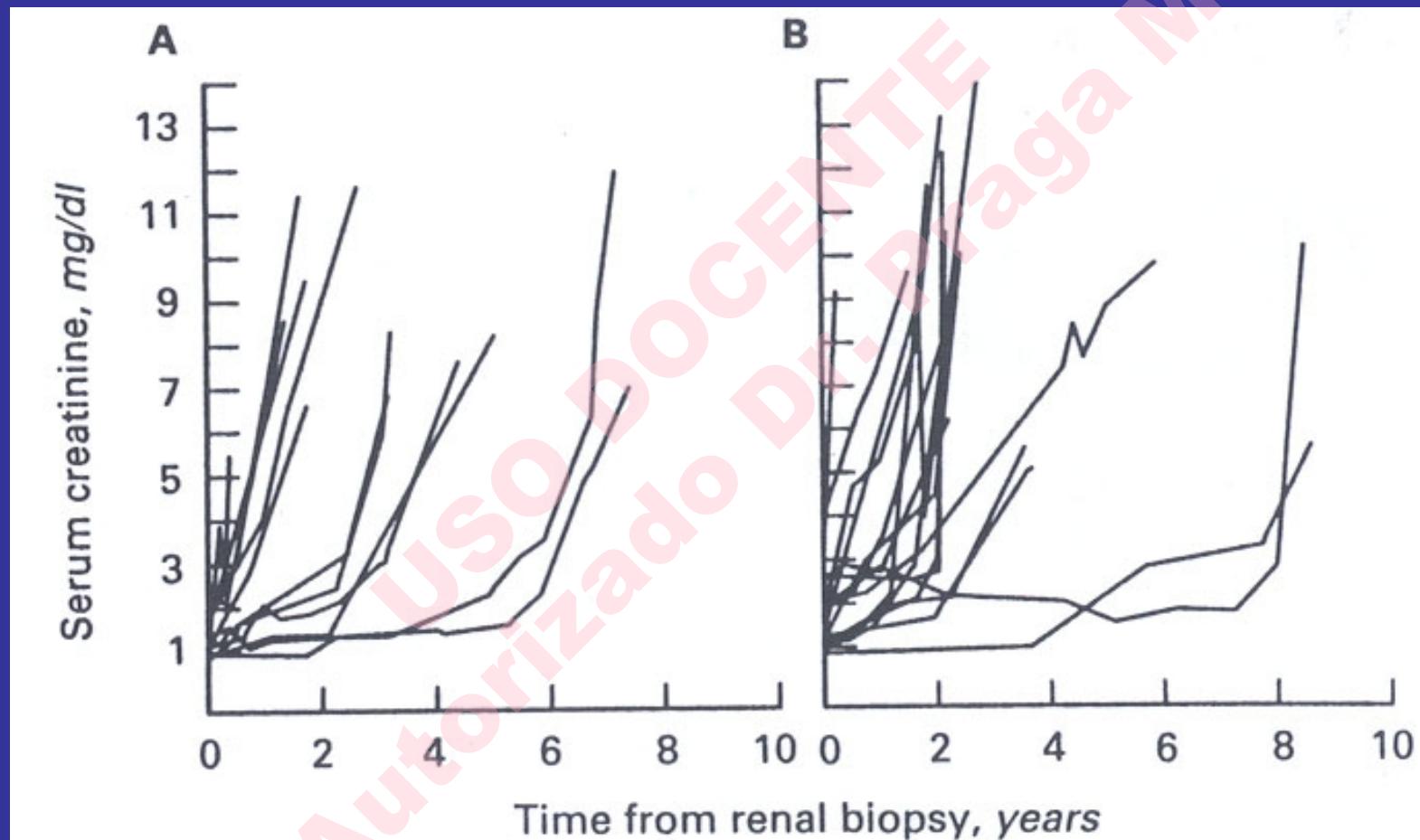


Membranous Nephropathy. Therapeutic Strategy



Idiopathic membranous nephropathy: The natural history of untreated patients

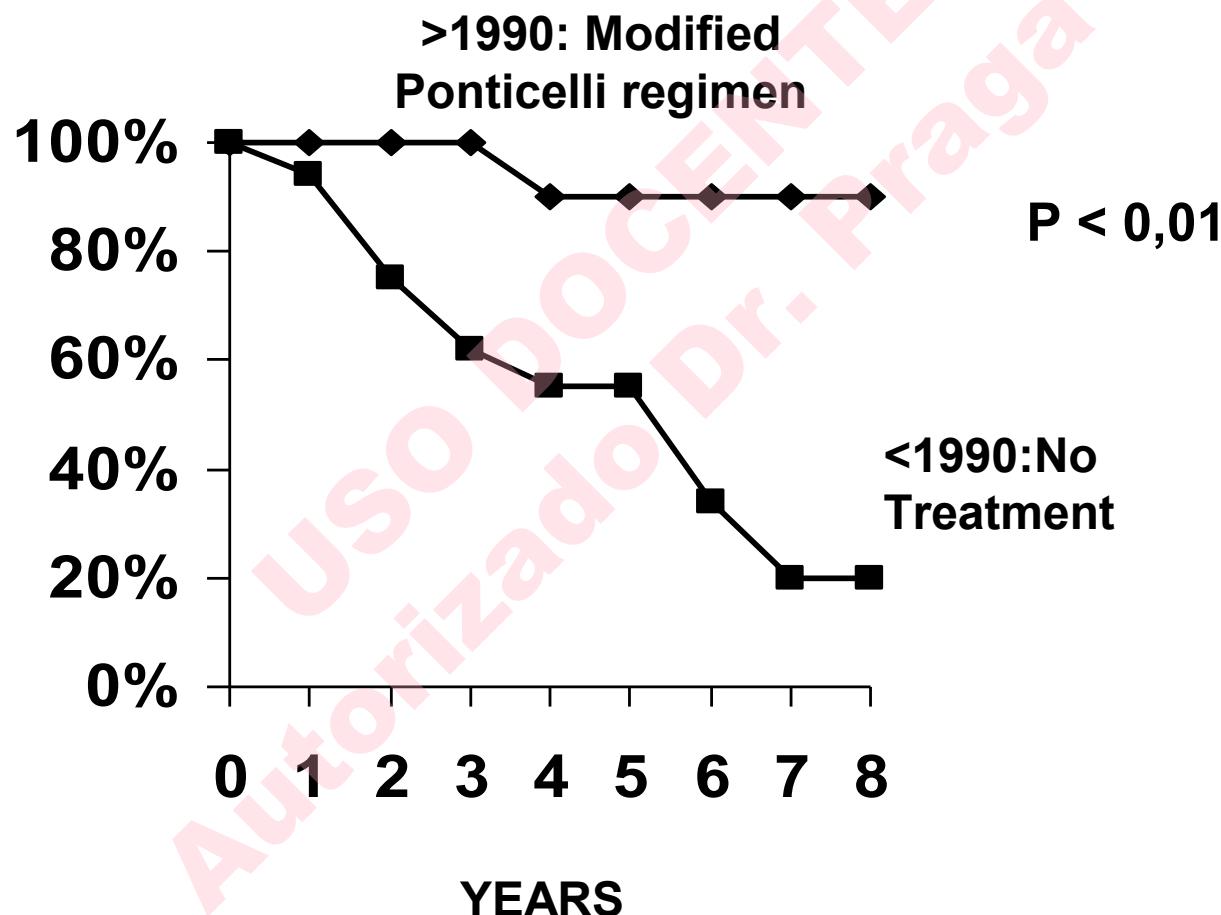
Donadio JV et al. Kidney Int 1988; 33: 708-715



28 patients (20%) developed ESRD, most of them in the first 2.5 years after diagnosis

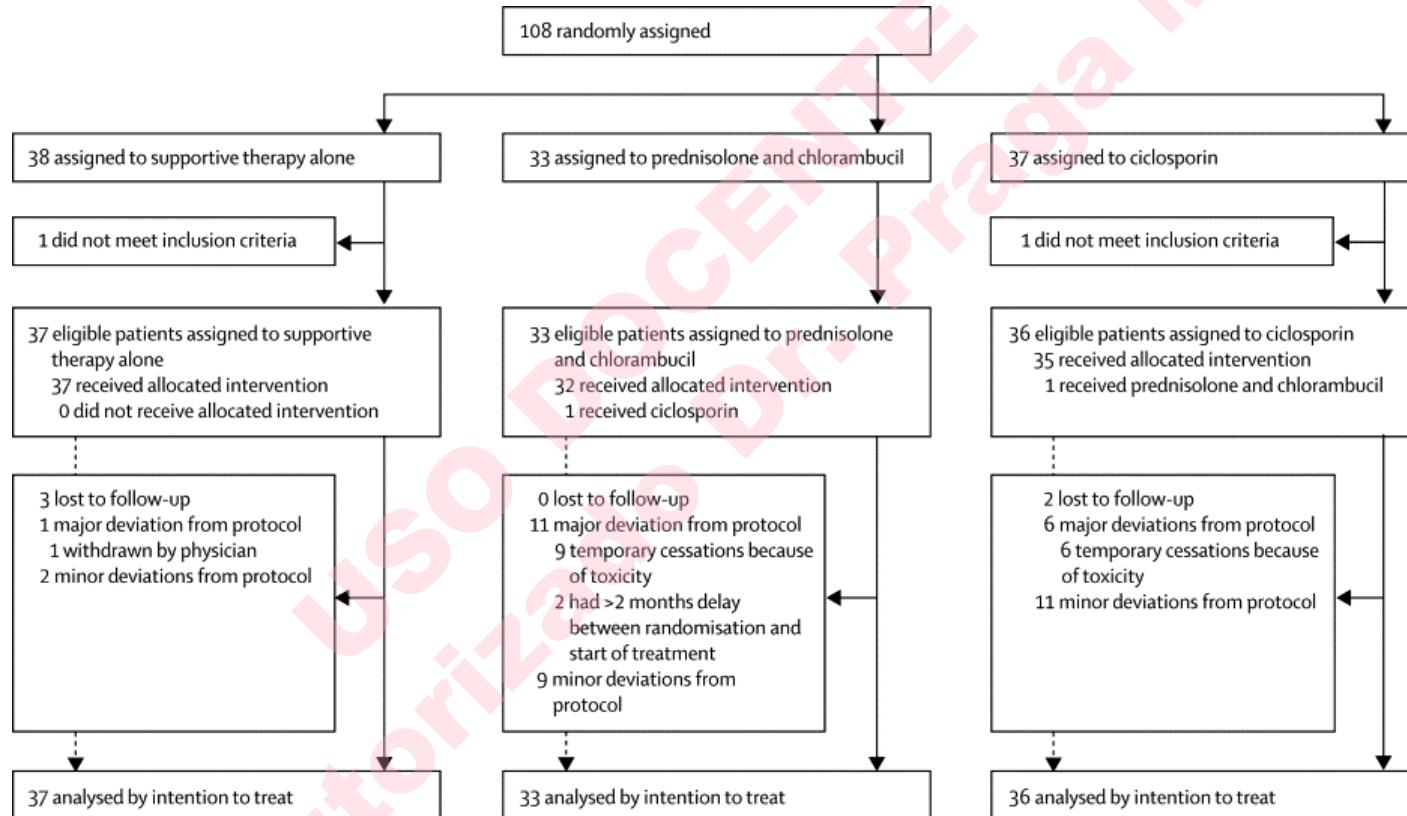
CONSERVATIVE VERSUS IMMUNOSUPPRESSIVE TREATMENT OF PATIENTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY AND DETERIORATING RENAL FUNCTION

Torres A, Domínguez-Gil B, Carreño A, Hernández E, Morales E, Segura J, González E, Praga M. *Kidney Int* 61:219-227, 2002

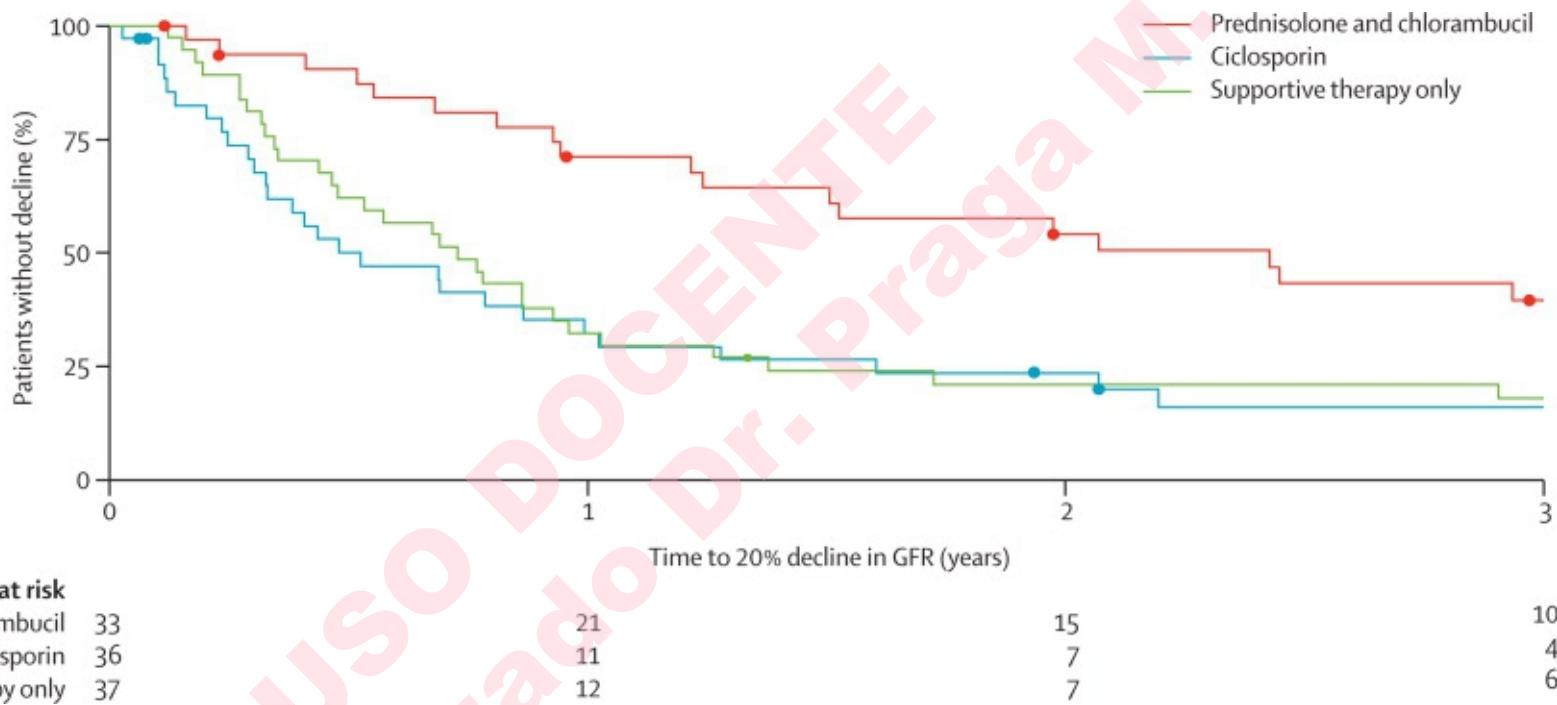


Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial.

Howman A et al. Lancet 381: 744-751, 2013



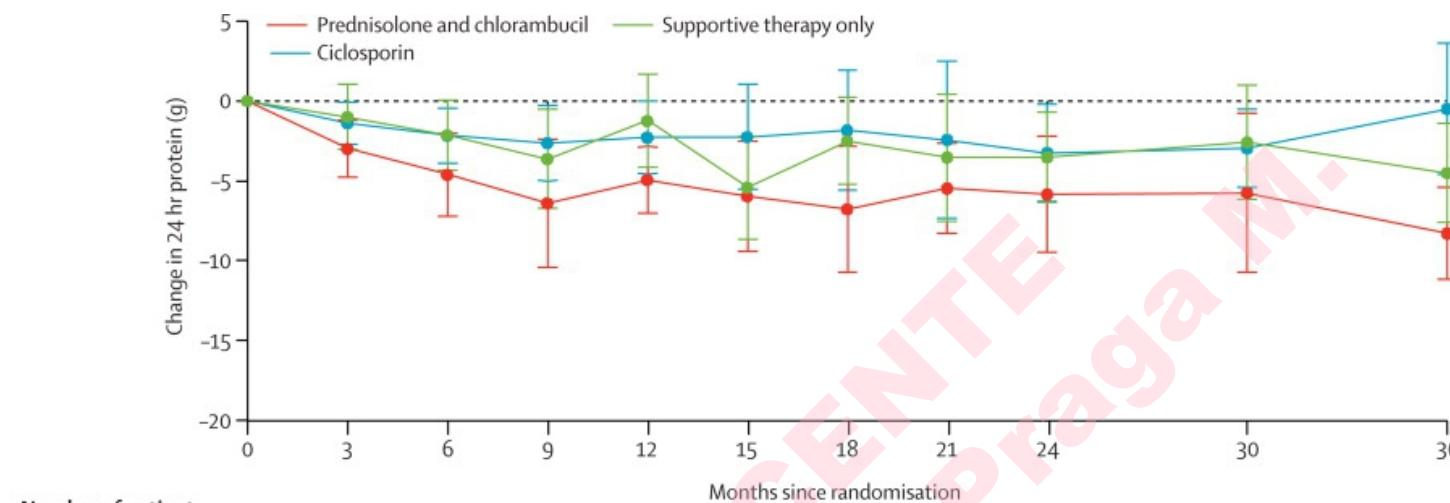
Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial.
Howman A et al. Lancet 381: 744-751, 2013



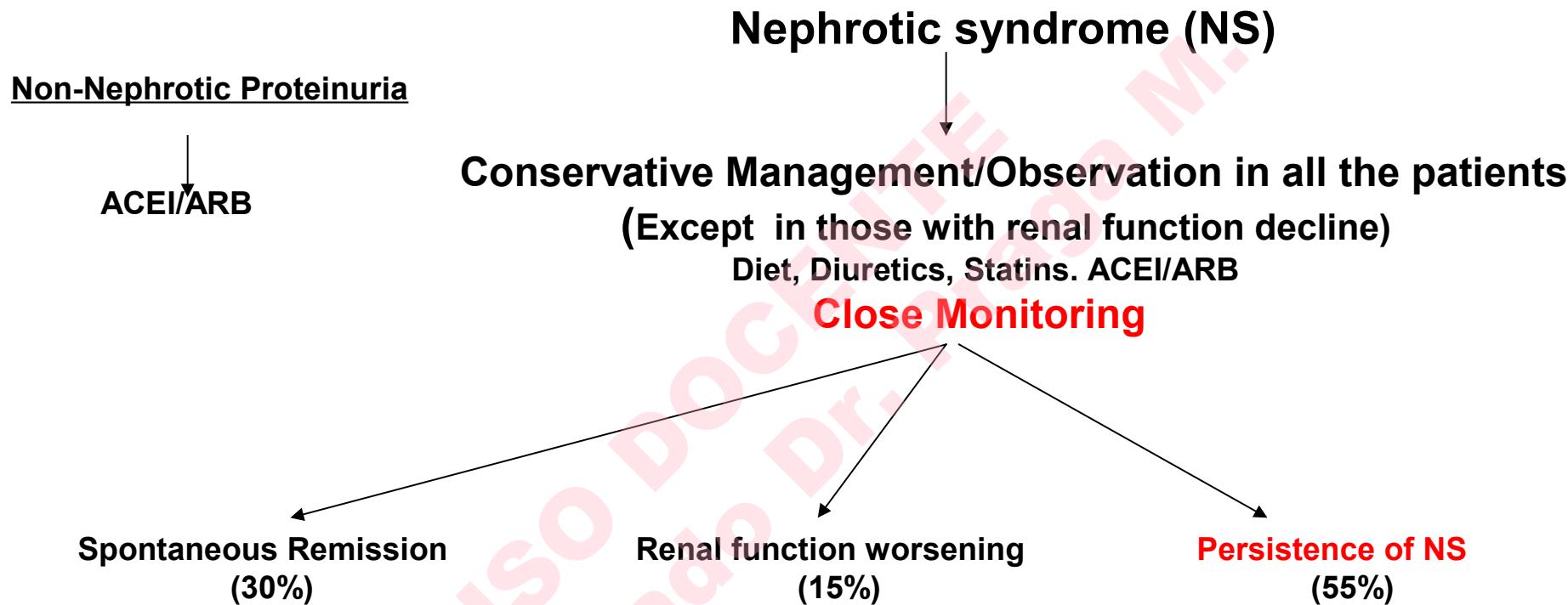
Conclusions: We conclude that six months' therapy with prednisolone and chlorambucil is superior to cyclosporine or supportive therapy alone in patients with IMN whose renal function is deteriorating. This effect is maintained to at least 3 years.

Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial.

Howman A et al. Lancet 381: 744-751, 2013

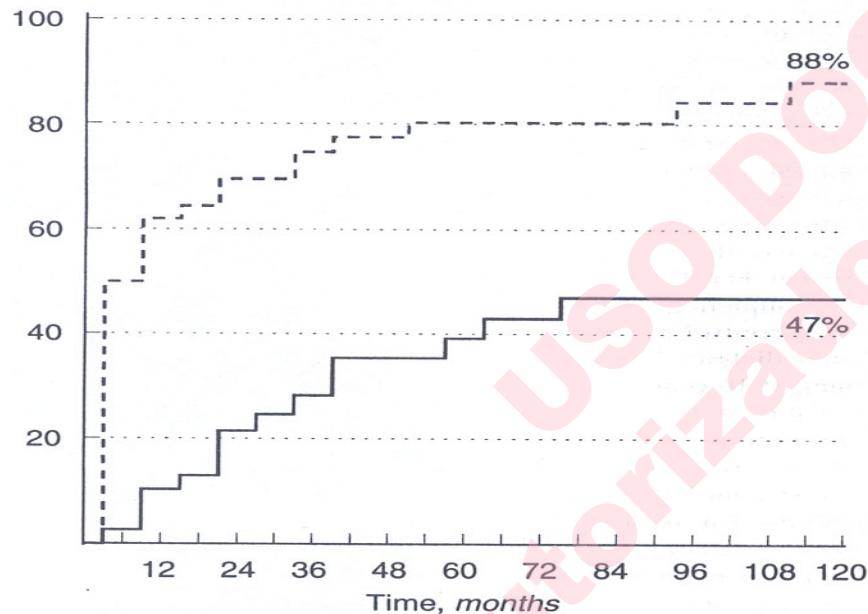


Membranous Nephropathy. Therapeutic Strategy

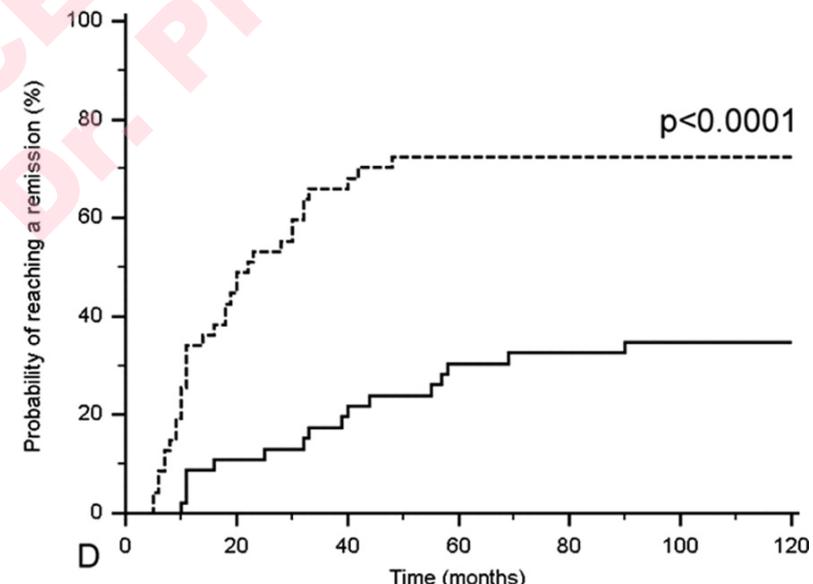


7. 3: Initial Therapy of IMN

7.3.1: We recommend that initial therapy consist of a **6 month course of alternating monthly cycles of oral and intravenous corticosteroids and oral alkylating agents.(1B)**



Steroids+Clorambucil
Ponticelli et al Kidney Int 1995



Steroids+Cyclophosphamide
Jha et al, JASN 2007

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

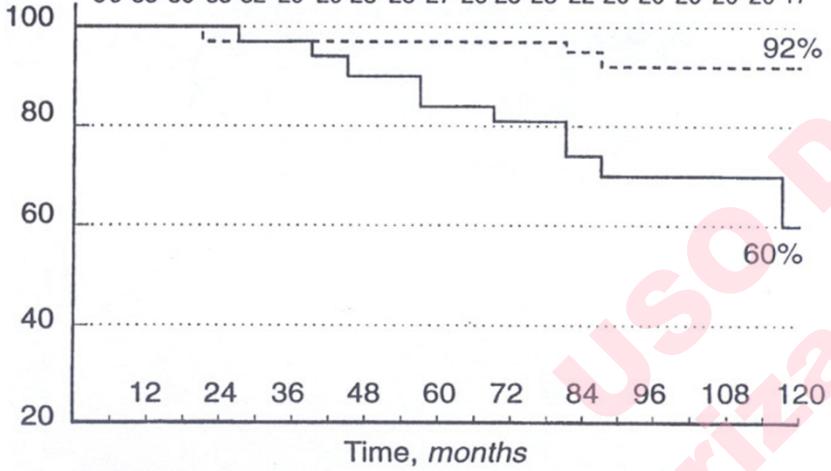
Ponticelli KI 1995

Treated Patients

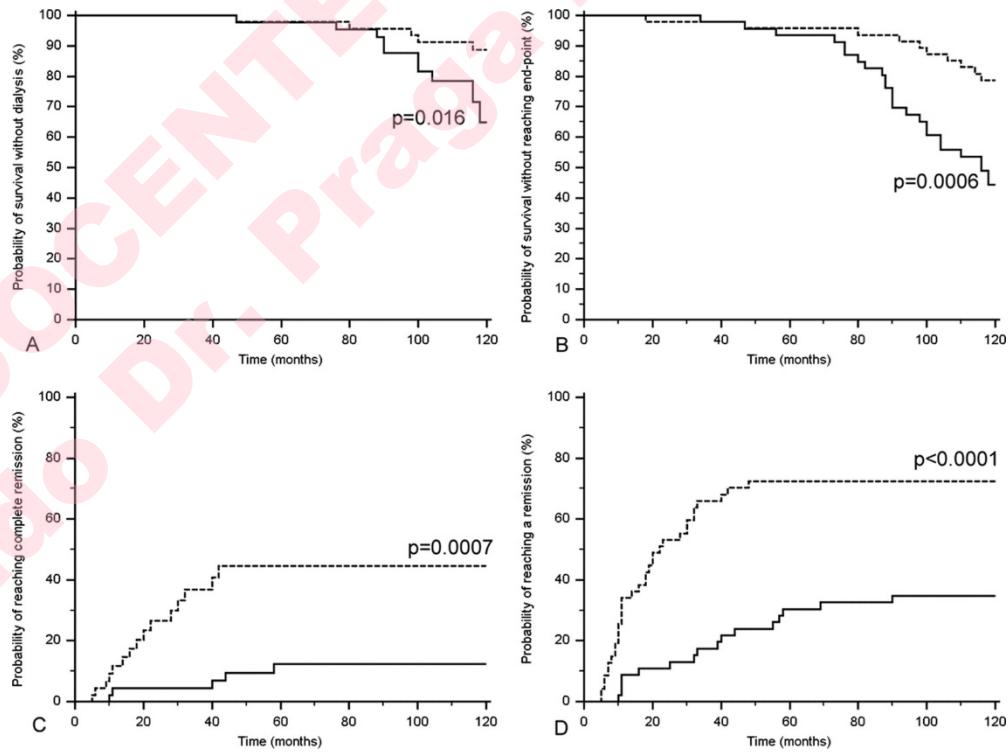
42 42 41 40 40 39 37 37 36 35 34 34 34 33 32 30 30 30 30 30

Untreated Patients

39 38 36 35 32 29 29 28 28 27 26 25 23 22 20 20 20 20 20 17



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)



Jha, V. et al. J Am Soc Nephrol

The Ponticelli Regimen

Month 1- 1g IV methylprednisolone daily for three doses, then oral methyprednisolone (0.5mg/kg/d) for 27 days

Month 2- Oral chlorambucil (CA ,0.15-0.2mg/kg/d) or oral Cyclophosphamide (CP, 2.0mg/kg/d) for 30days*

Month 3- Repeat Month 1

Month 4- Repeat Month 2

Month 5- Repeat Month 1

Month 6- Repeat Month 2

(*Monitor every 2 weeks for 2 months, then every month for 6 months, with Scr, urinary protein excretion, serum albumin, and white blood cells count. If total leukocyte count falls to <3500/mm³ then CH or CYC withheld until recovery to >4000/mm³)



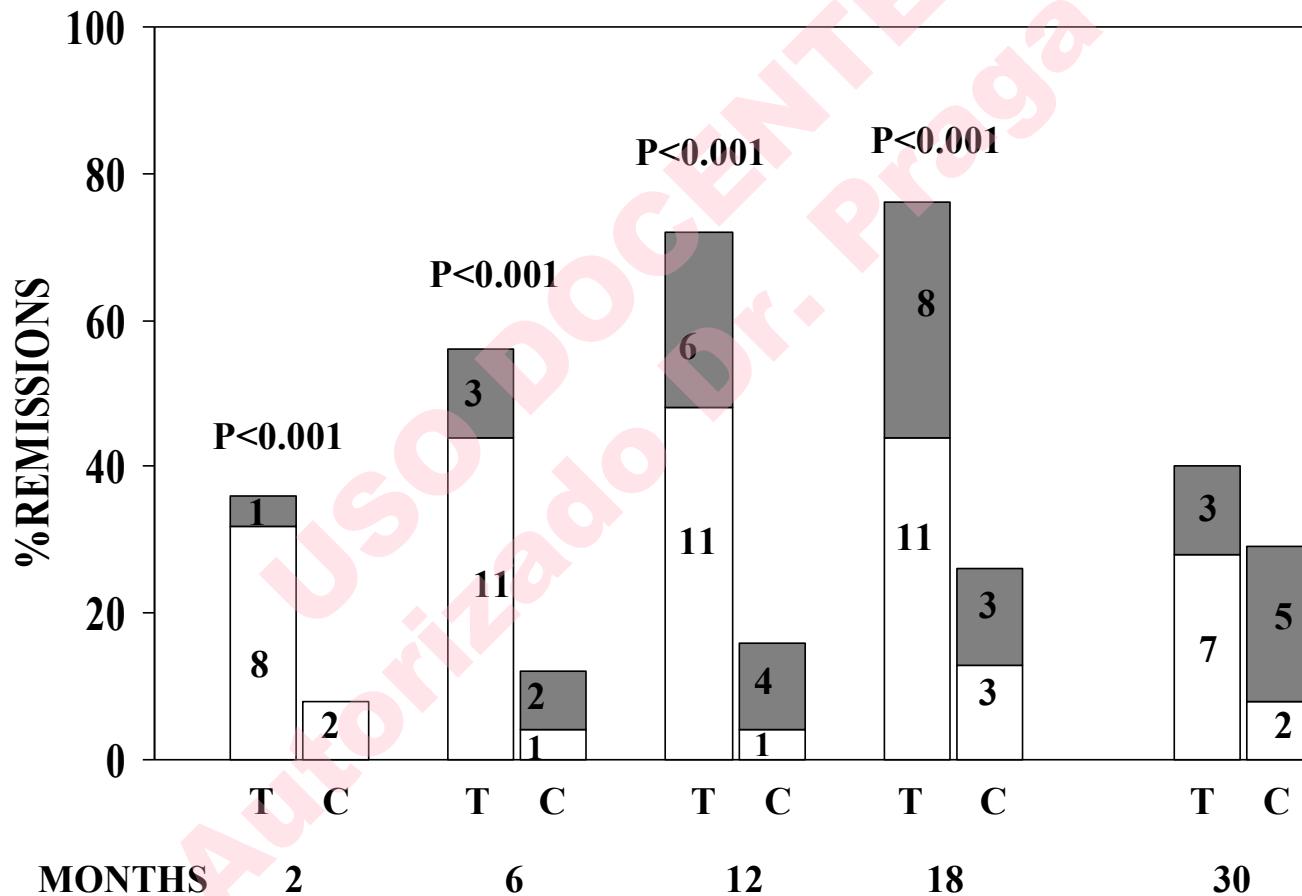
7.4: Alternative Regimens for the Initial Therapy of IMN – Calcineurin Inhibitors (CNI)

7.4.1: We recommend that CsA or Tac be used for a period of at least 6 months in patients who meet the criteria for initial therapy (as described in 7.1.2), but who choose not to receive the cyclical corticosteroid-alkylating agent regimen or who have contraindications to this regimen. (1C)

Study		Complete Remission (CR)	Partial Remission (PR)	Remissions (CR+PR)
Cattran Kidney Int 2001	Cyclosporin	7%	68%	75%
	Control	4%	17%	19%
Praga Kidney Int 2007	Tacrolimus	32%	44%	76%
	Control	13%	13%	26%

Tacrolimus monotherapy in membranous nephropathy: A randomized controlled trial

M Praga¹, V Barrio², G Fernández Juárez² and J Luño³, For the GRUPO ESPAÑOL DE ESTUDIO DE LA NEFROPATÍA MEMBRANOSA (Members of the Group listed at the end of the paper)



Main limitation of CNI in the treatment of IMN: High rates of relapses after their discontinuation

Study		CR	PR	Remission (Total)	Relapse
Cattran Kidney Int 2001	Cyclosporin	7%	68%	75%	48%
	Control	4%	17%	19%	
Praga Kidney Int 2007	Tacrolimus	32%	44%	76%	47%
	Control	13%	13%	26%	

Original Article

Predictors of response and relapse in patients with idiopathic membranous nephropathy treated with tacrolimus

Jara Caro¹, Elena Gutiérrez-Solis¹, Jorge Rojas-Rivera², Irene Agraz³, Natalia Ramos³, Cristina Rabasco⁴, Mario Espinosa⁴, Alfonso Valera⁵, Mónica Martín⁵, Miguel Ángel Frutos⁶, Lara Perea⁶, Gema Fernández Juárez⁷, Javier Ocaña⁷, David Arroyo⁸, Marian Goicoechea⁸, Laura Fernández⁹, Aniana Oliet¹⁰, Yolanda Hernández¹¹, Ana Romera¹², Alfons Segarra³ and Manuel Praga^{1,13} for the Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología (GLOSEN)

Table 2. Factors predicting remission (either complete or partial) of nephrotic syndrome after tacrolimus treatment

Variables in the model	Univariate model			Multivariate model				
	HR	95% CI	P	β	SE	HR	95% CI	P-value
Sex (female versus male)	1.33	0.87–2.03	0.185	–	–	–	–	–
SCr at kidney biopsy	0.80	0.29–2.20	0.669	–	–	–	–	–
Proteinuria at kidney biopsy	0.92	0.87–0.98	0.004	–	–	–	–	–
SCr at the onset of tacrolimus therapy	0.93	0.43–2.02	0.856	–	–	–	–	–
Proteinuria at the onset of tacrolimus therapy ^a	0.92	0.87–0.97	0.003			NA		
Proteinuria at the onset of tacrolimus therapy ^b								0.014
Q1: lowest quartile (≤ 5 g/day)	Reference category			Reference category				
Q2: second quartile (5.1–7.6 g/day)	0.78	0.45–1.36	0.378	–0.185	0.298	0.83	0.46–1.49	0.534
Q3: third quartile (7.7–10.6 g/day)	0.47	0.27–0.83	0.009	–0.677	0.291	0.51	0.29–0.90	0.020
Q4: highest quartile (≥ 10.7 g/day)	0.41	0.23–0.73	0.002	–0.862	0.305	0.42	0.23–0.77	0.005

Original Article

Predictors of response and relapse in patients with idiopathic membranous nephropathy treated with tacrolimus

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Table 6. Factors associated with relapses

Variables in the model	Univariate model			Multivariable model				
	HR	95% CI	P-value	β	SE	HR	95% CI	P-value
Proteinuria at the onset of tacrolimus tapering (g/day)	1.11	0.84–1.47	0.453	–	–	–	–	–
Proteinuria at tacrolimus withdrawal (g/day)	1.39	0.86–2.23	0.182	–	–	–	–	–
Duration of tacrolimus tapering (months)	0.92	0.85–0.99	0.042	−0.132	0.048	0.88	0.79–0.96	0.007
PR ^a	3.55	0.45–27.76	0.23	2.808	1.382	16.58	1.10–249.08	0.042
CR	0.34	0.11–1.07	0.065	–	–	–	–	–

Conclusions. Tacrolimus monotherapy is an effective and safe option for the treatment of MN with stable renal function. Relapses are frequent in patients with PR and can be partially prevented by a longer tapering period.

Rituximab to prevent NS relapse when discontinuing Calcineurin Inhibitors

PROTOCOL

- Patients with previous NS relapse after TAC withdrawal or Patients with Proteinuria >2-3 g/d at the onset of TAC tapering:
- Rituximab:
375 mg/m² weekly x 4, **or** 1 g /15 days x2,
or 1 g (single dose)
- TAC tapering for 3-6 months after RTX treatment

SUCCESSFUL TREATMENT WITH RITUXIMAB OF MEMBRANOUS GLOMERULONEPHRITIS WITH DEPENDENCE OF CALCINEURIN INHIBITORS. Segarra et al Clin JASN 2009.

- 13 patients with IMN and long-term dependence on treatment with TAC
- RTX (375 mg/m²) weekly x 4, while the patient was on partial remission with TAC
- TAC tapering for 3-6 months after RTX treatment

Evolution of urinary protein excretion

	Basal	3 m	6 m	9 m	12 m	18 m	24 m	30 m
Mean Proteinuria (g/d)	2,41	,99 *	,83 *	,65*	,68*	1,29**	,77*	,89*

Rituximab in IMN

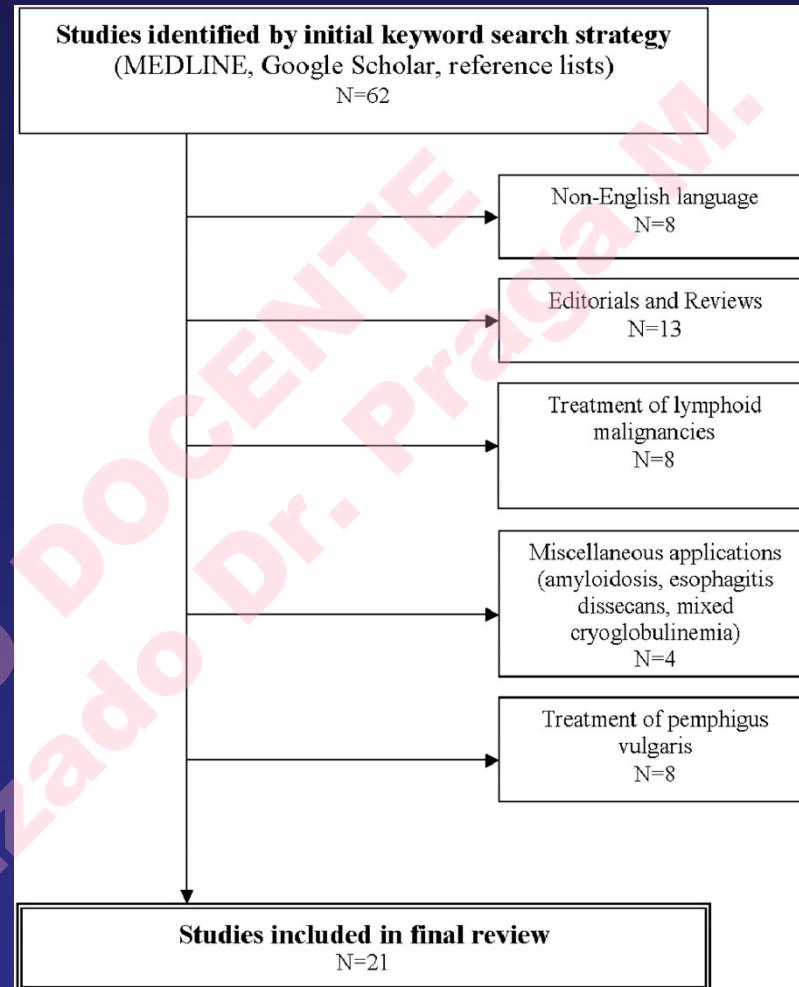
Systematic Review

RTX

(375 mg/m² for 4 wk
or 1 g on days 1 and 15):

15 to 20%
rate of complete remission
35 to 40%
rate of partial remission.

The drug was well tolerated
with minimal adverse events.

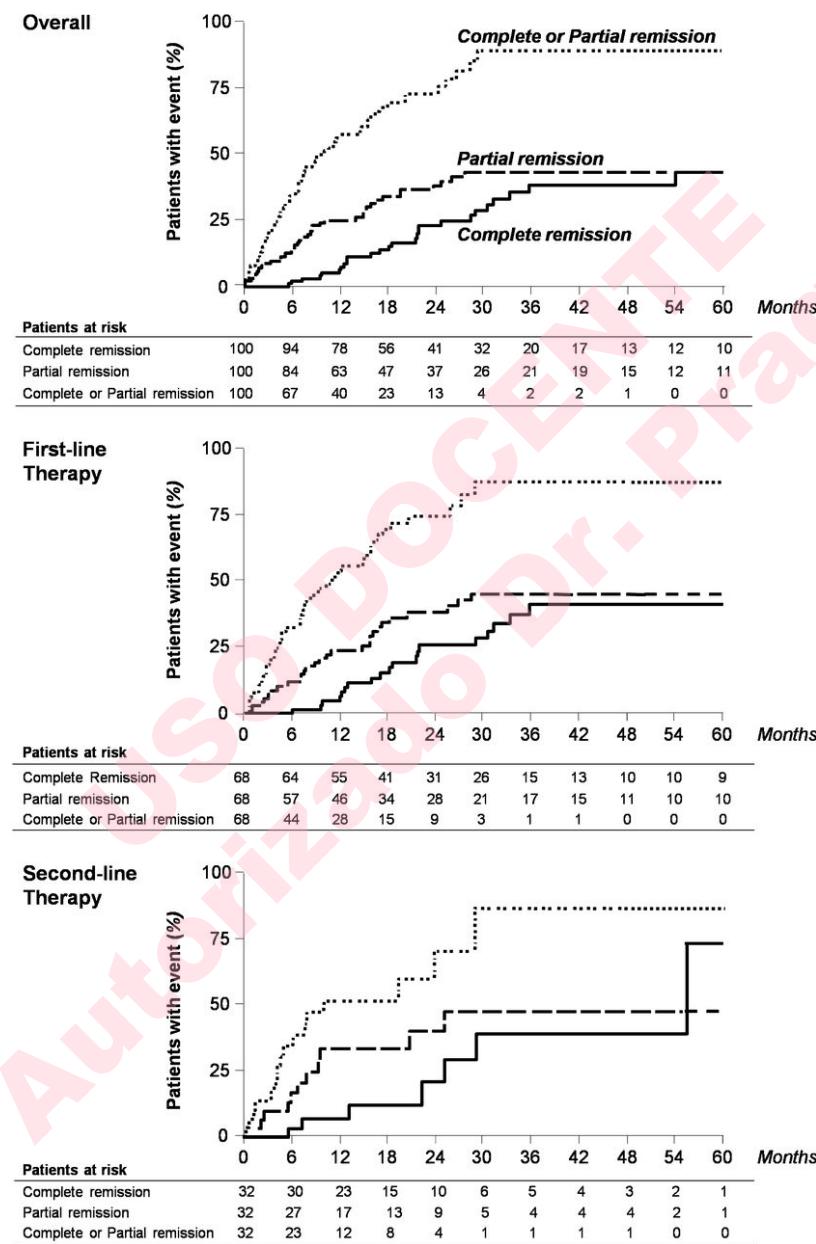


Bomback, A. S. et al. Clin J Am Soc Nephrol 2009;4:734-744

Rituximab in Idiopathic Membranous Nephropathy

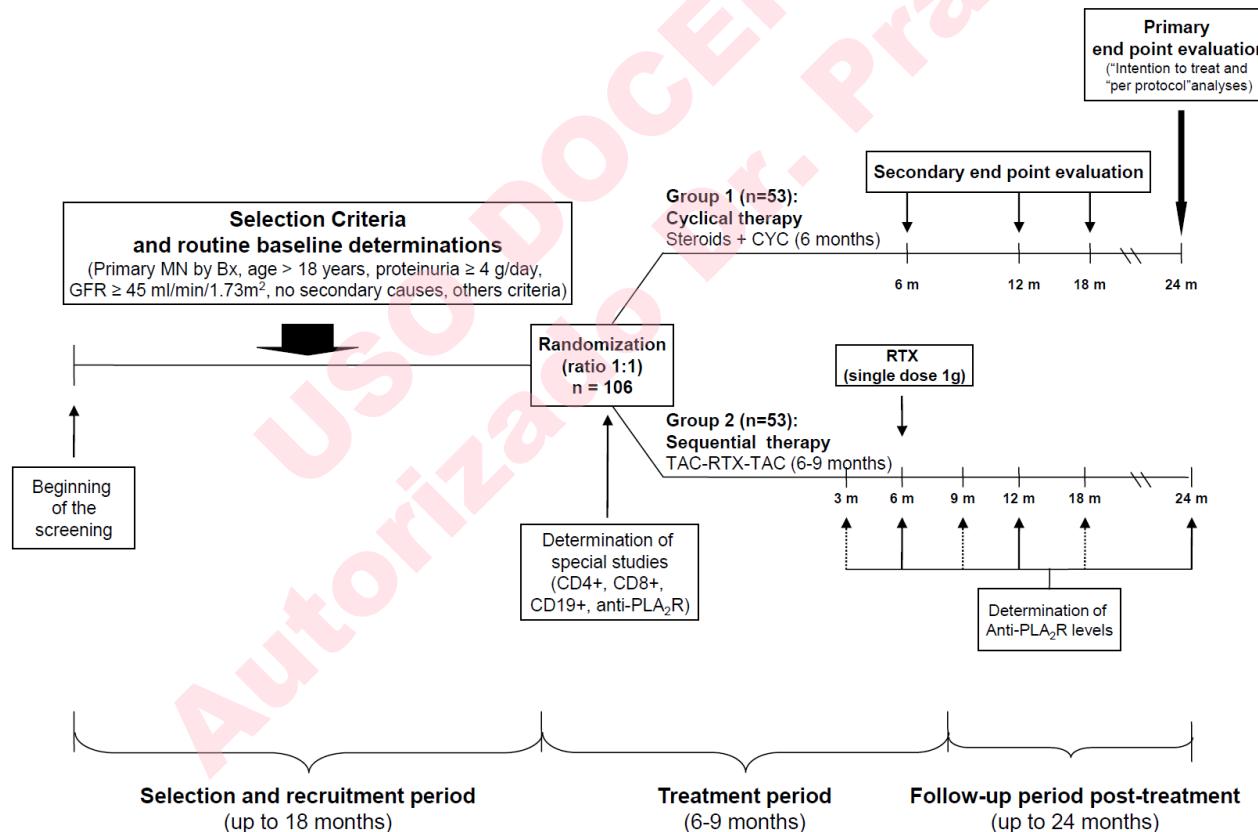
Piero Ruggenenti,^{*†} Paolo Cravedi,^{*} Antonietta Chianca,^{*} Annalisa Perna,^{*} Barbara Ruggiero,^{*} Flavio Gaspari,^{*} Alessandro Rambaldi,[‡] Maddalena Marasà,^{*} and Giuseppe Remuzzi^{*†}

JASN 2012;23:1416-1425



RCT with Rituximab (RTx)

- MENTOR: Cyclosporin vs RTx
- STARMEN: Ponticelli Regimen (Corticosteroids+Cyclophosphamide) vs Tacrolimus-RTx



Mycophenolate Mofetil Monotherapy in Membranous Nephropathy: A 1-Year Randomized Controlled Trial

Bertrand Dussol, MD,¹ Sophie Morange, MD,² Stéphane Burtey, MD,¹ Monica Indreies, MD,¹

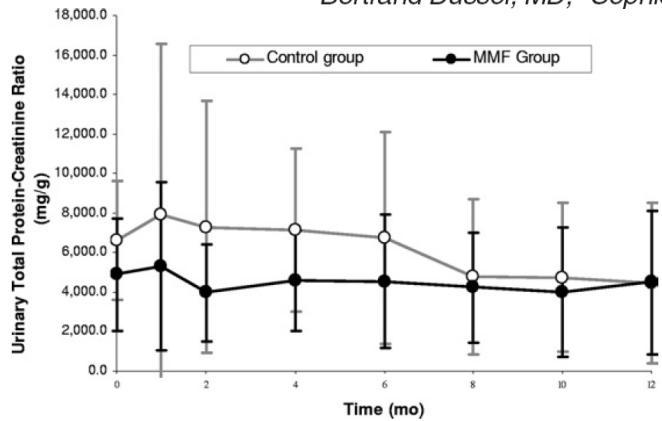


Figure 3. Course of mean proteinuria over creatinuria ratios (mg/g) during the study. All patients were available at each time for these measurements. Abbreviation: MMF, mycophenolate mofetil.

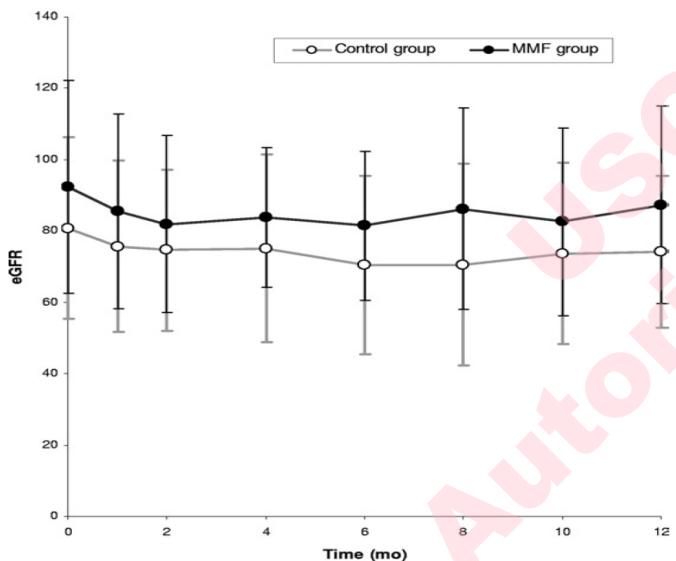


Figure 5. Course of estimated glomerular filtration rates (eGFRs) during the study. All patients were available at each time for eGFR measurements. Abbreviation: MMF, mycophenolate mofetil.

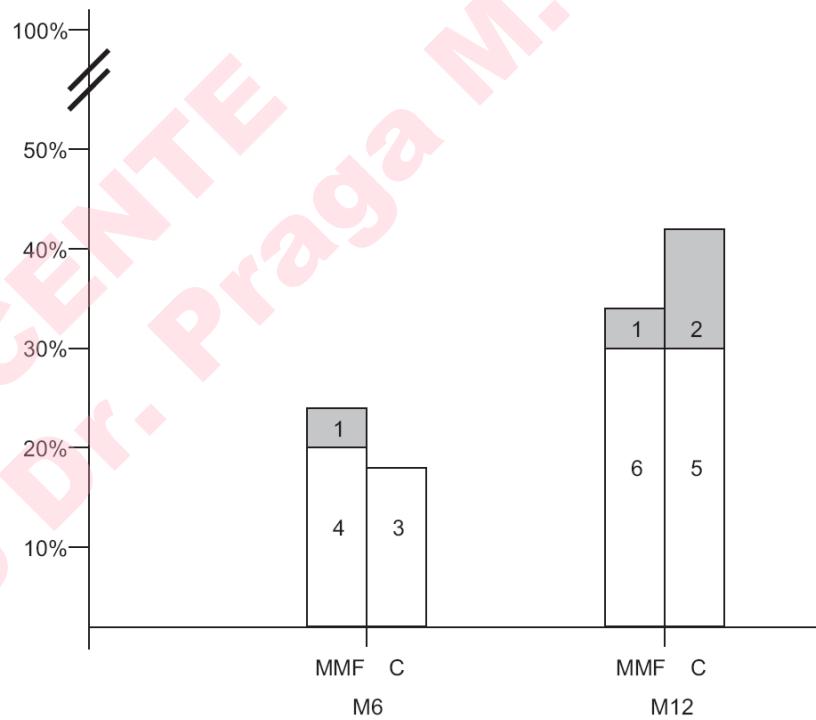
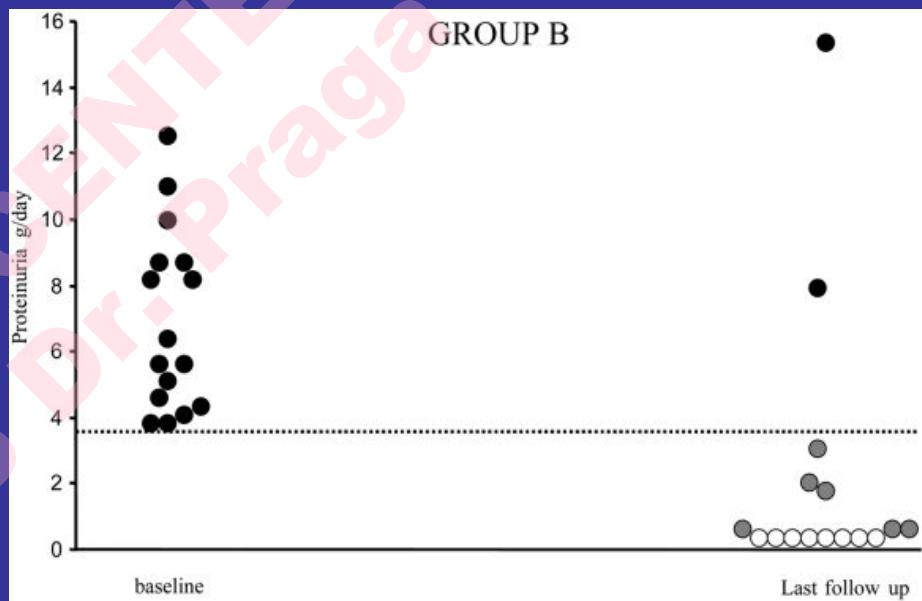
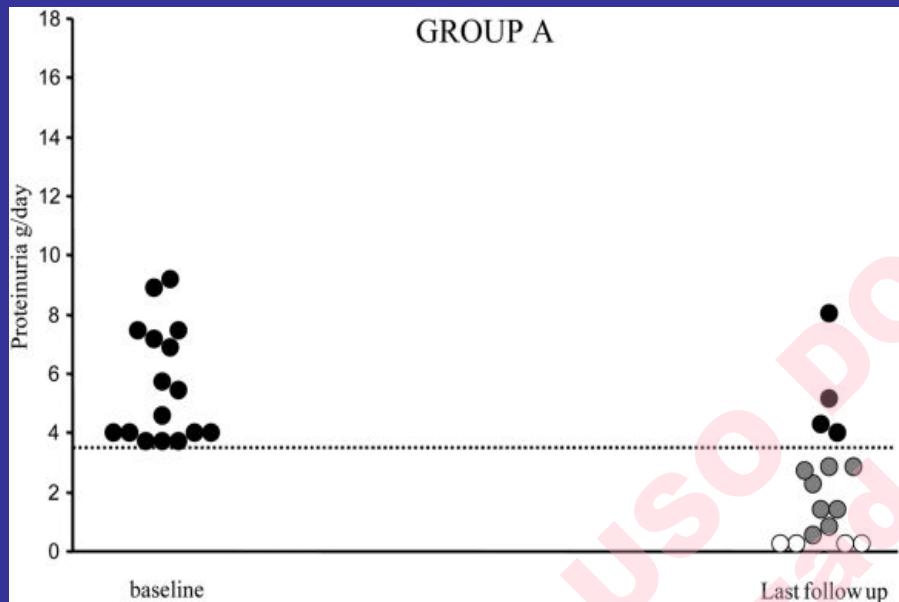


Figure 4. Percentages of complete (grey) and partial (white) remissions in the mycophenolate mofetil (MMF) and control (C) groups. Numbers within columns indicate total numbers of patients in complete and partial remission in both groups. Abbreviation: M, month.

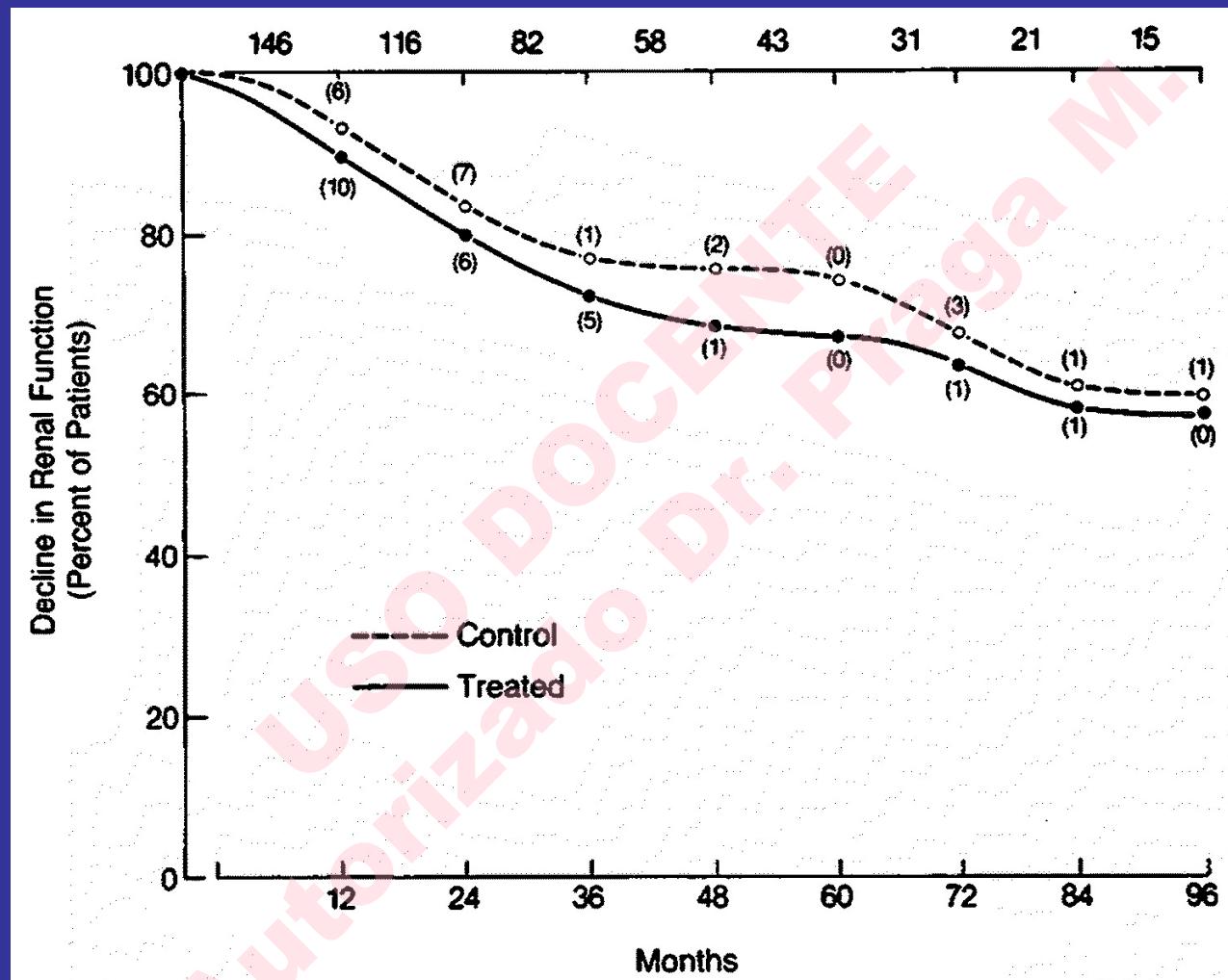
(Ponticelli's treatment)

(Adrenocorticotrophic hormone-ACTH-
i.m. twice a week for one year)



A randomized pilot trial comparing methylprednisolone plus a citotoxic Agent versus synthetic adrenocorticotrophic hormone in Idiopathic membranous nephropathy
Ponticelli C et al. AJKD 47: 233, 2006

Decline in Renal Function in Patients Treated with Prednisone for Idiopathic Membranous Nephropathy and in Controls.

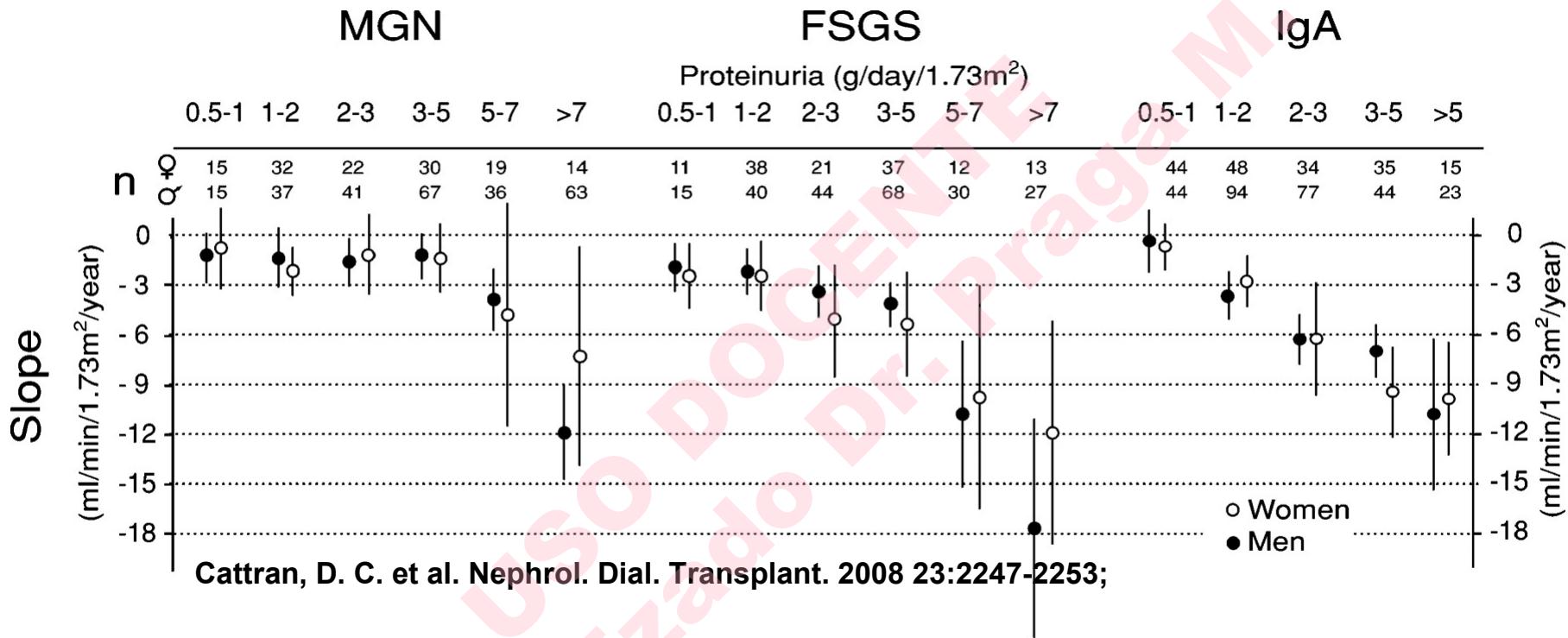


Cattran DC et al. N Engl J Med
1989;320:210-215.



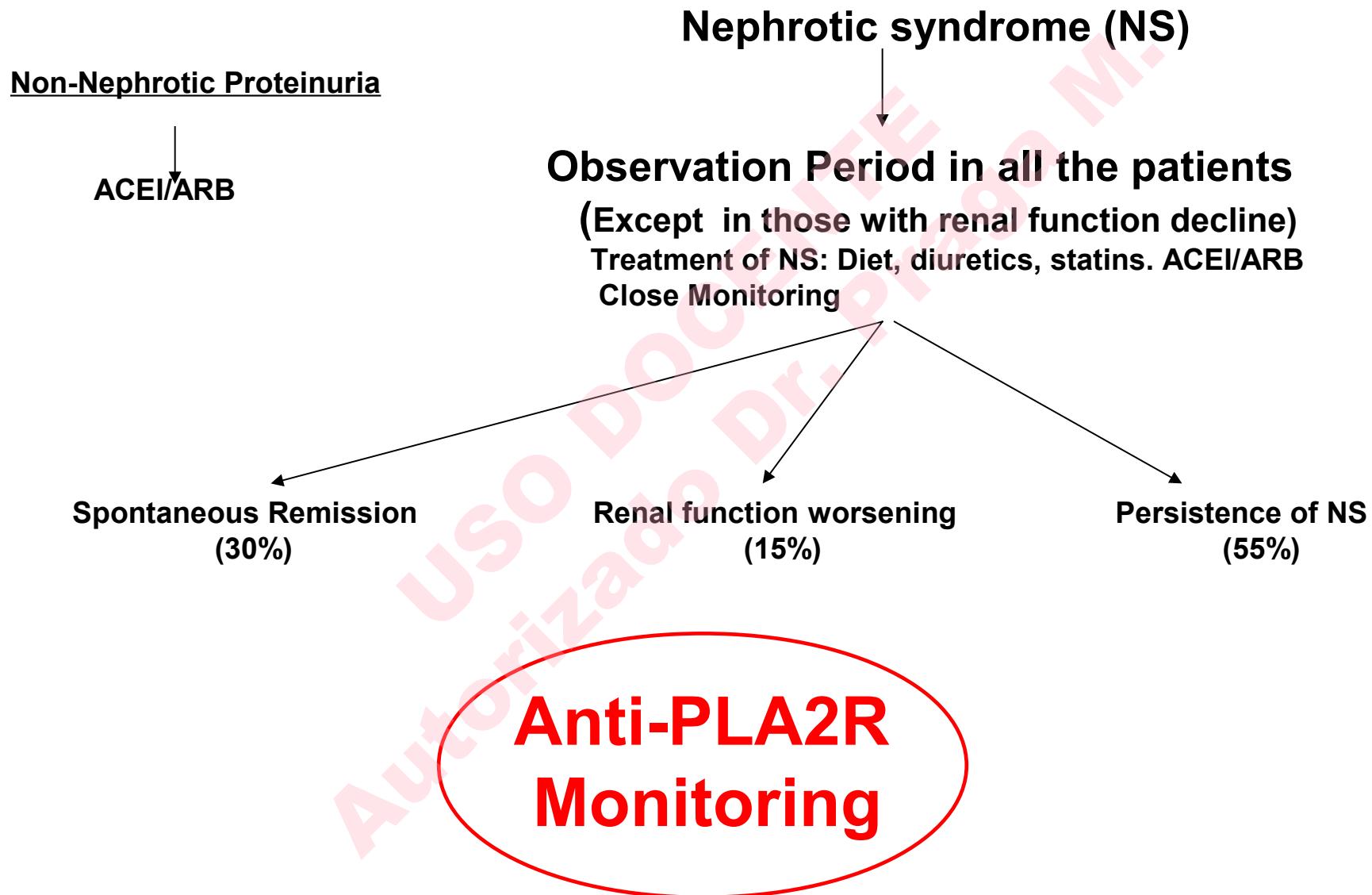
The NEW ENGLAND
JOURNAL of MEDICINE

Interaction between time average proteinuria and sex in relation to the rate of renal function decline in MGN, FSGS and IgA nephropathy



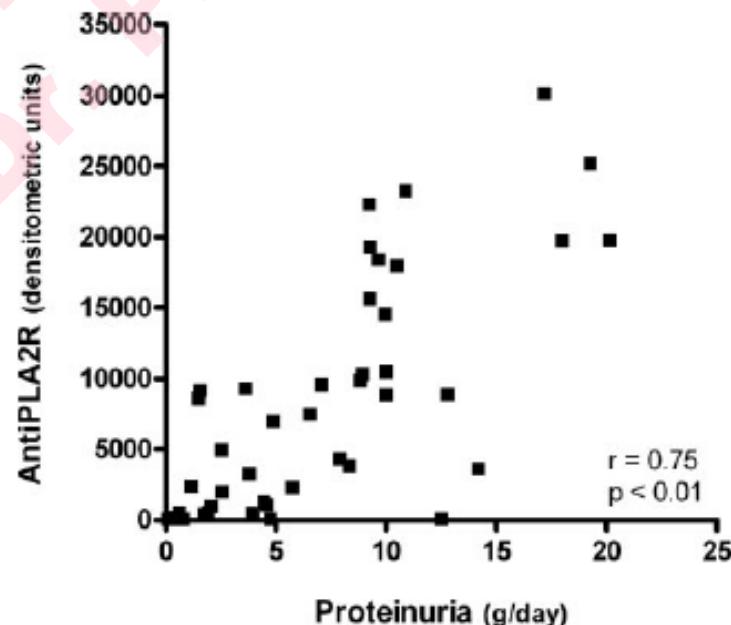
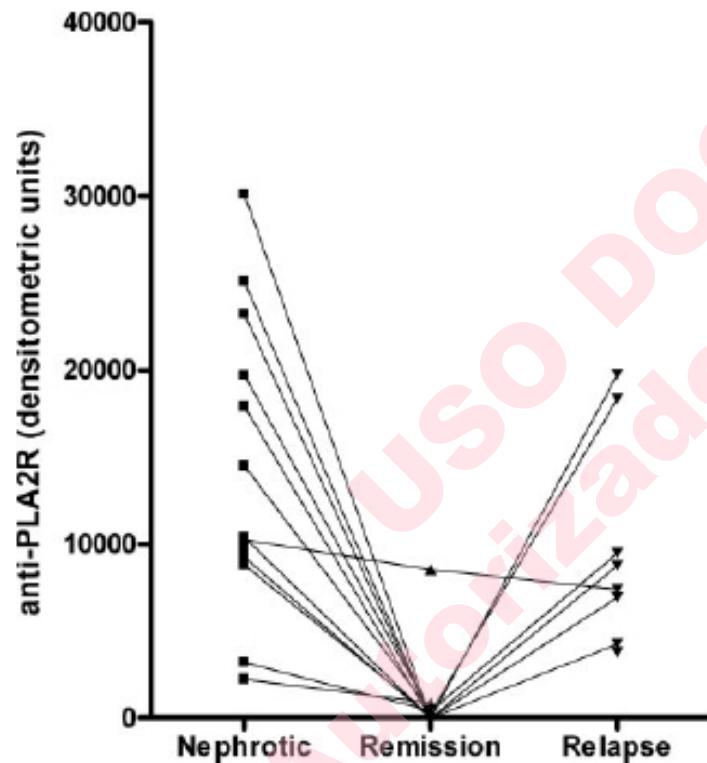
Proteinuria Target for MN : <3.5 g/day

Membranous Nephropathy. Therapeutic Strategy



Anti-Phospholipase A₂ Receptor Antibodies Correlate with Clinical Status in Idiopathic Membranous Nephropathy

Julia M. Hofstra,* Laurence H. Beck, Jr.,† David M. Beck,† Jack F. Wetzels,* and David J. Salant†



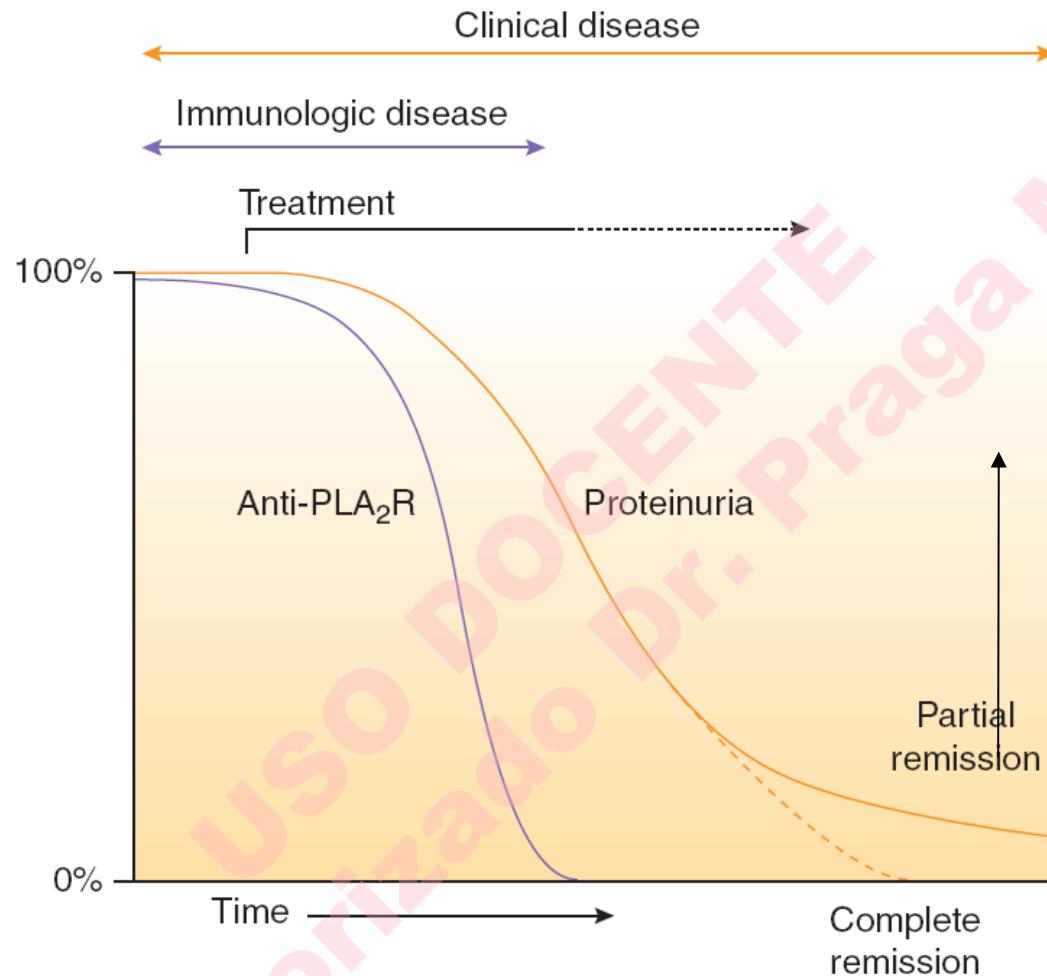
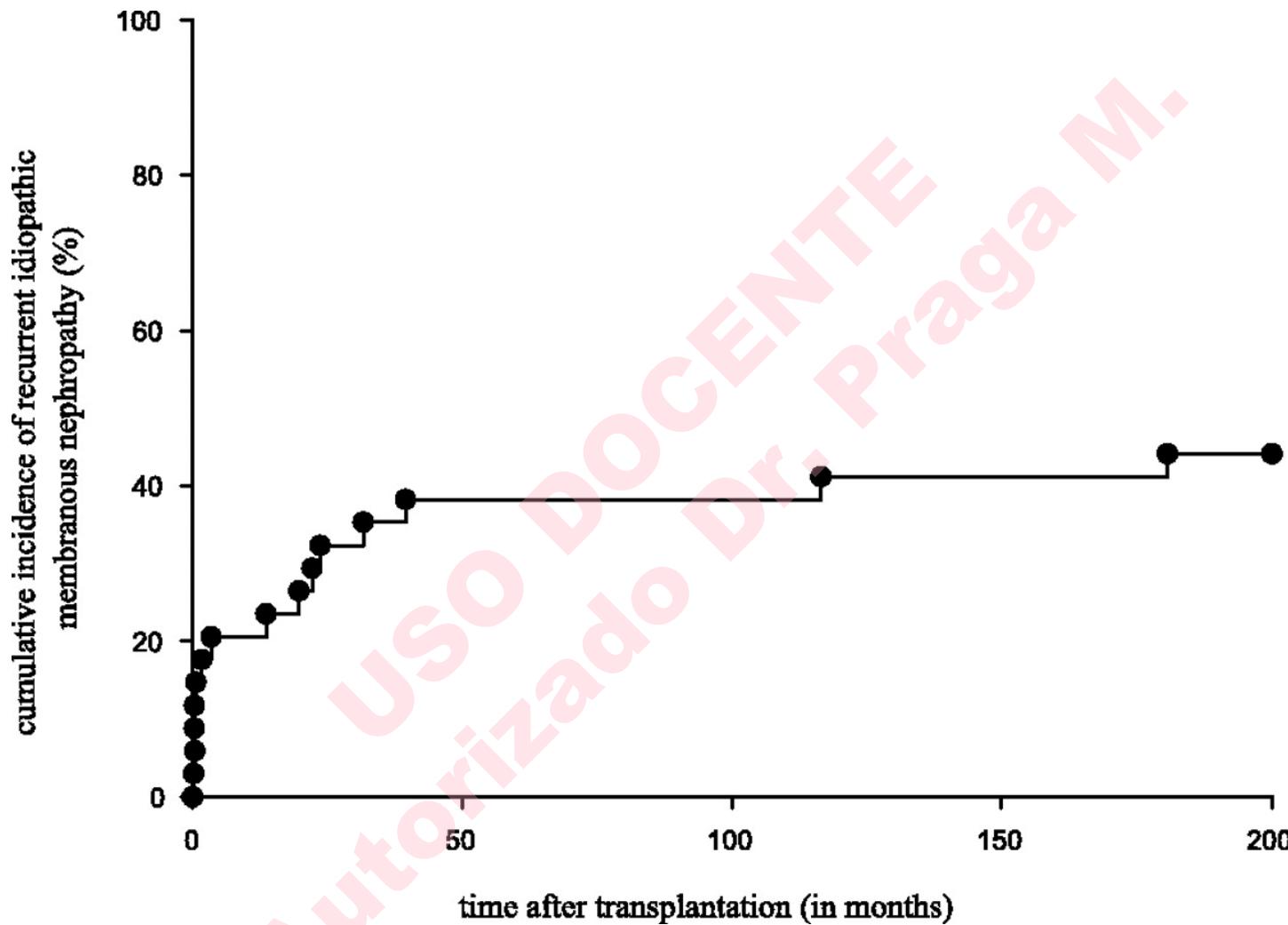


Figure 1 | Relationship between clinical disease (proteinuria) and immunological activity (circulating anti-PLA₂R) in idiopathic membranous nephropathy.

Beck LH, Salant DJ. Membranous nephropathy: recent travels and new road ahead. Kidney Int 2010.

Cumulative incidence of recurrent iMN was constructed using Kaplan-Meier plots.



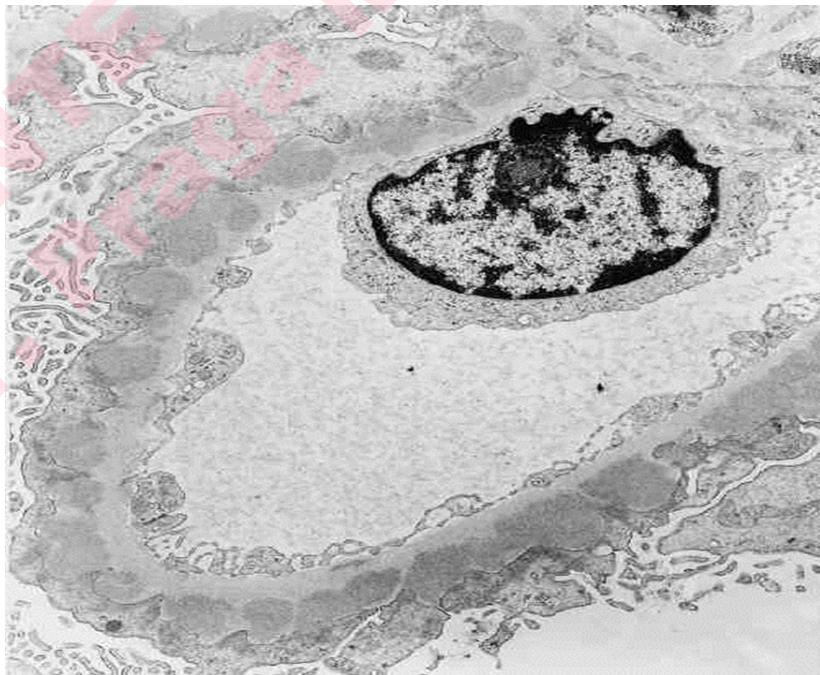
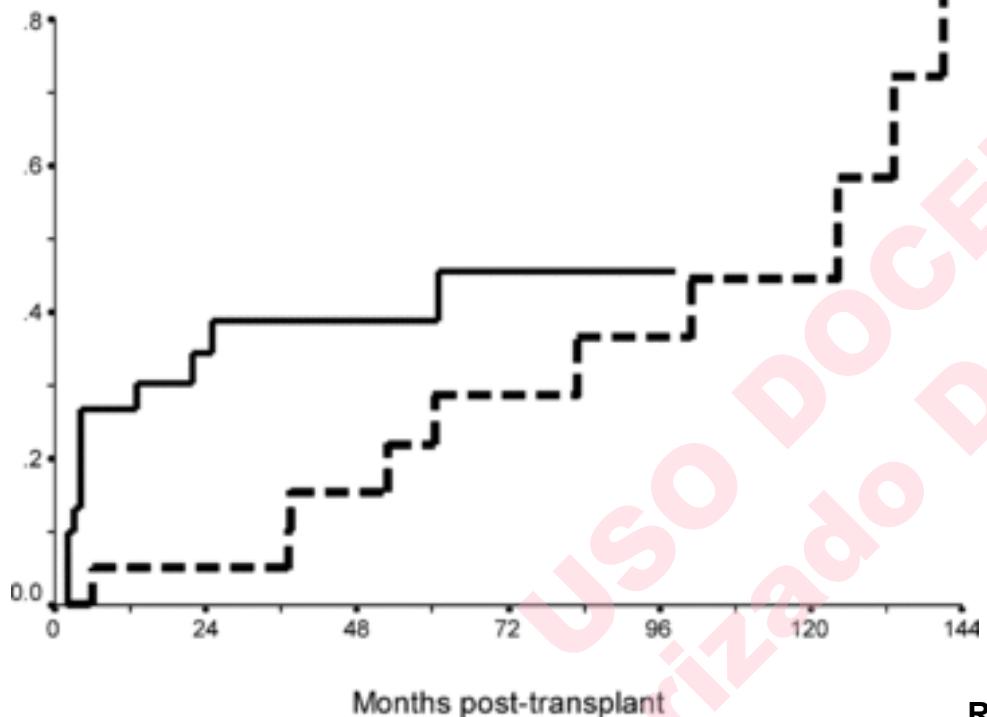
Sprangers B et al. CJASN 2010;5:790-797

CJASN

Recurrent Idiopathic Membranous Nephropathy: Early Diagnosis by Protocol Biopsies and Treatment with Anti-CD20 Monoclonal Antibodies

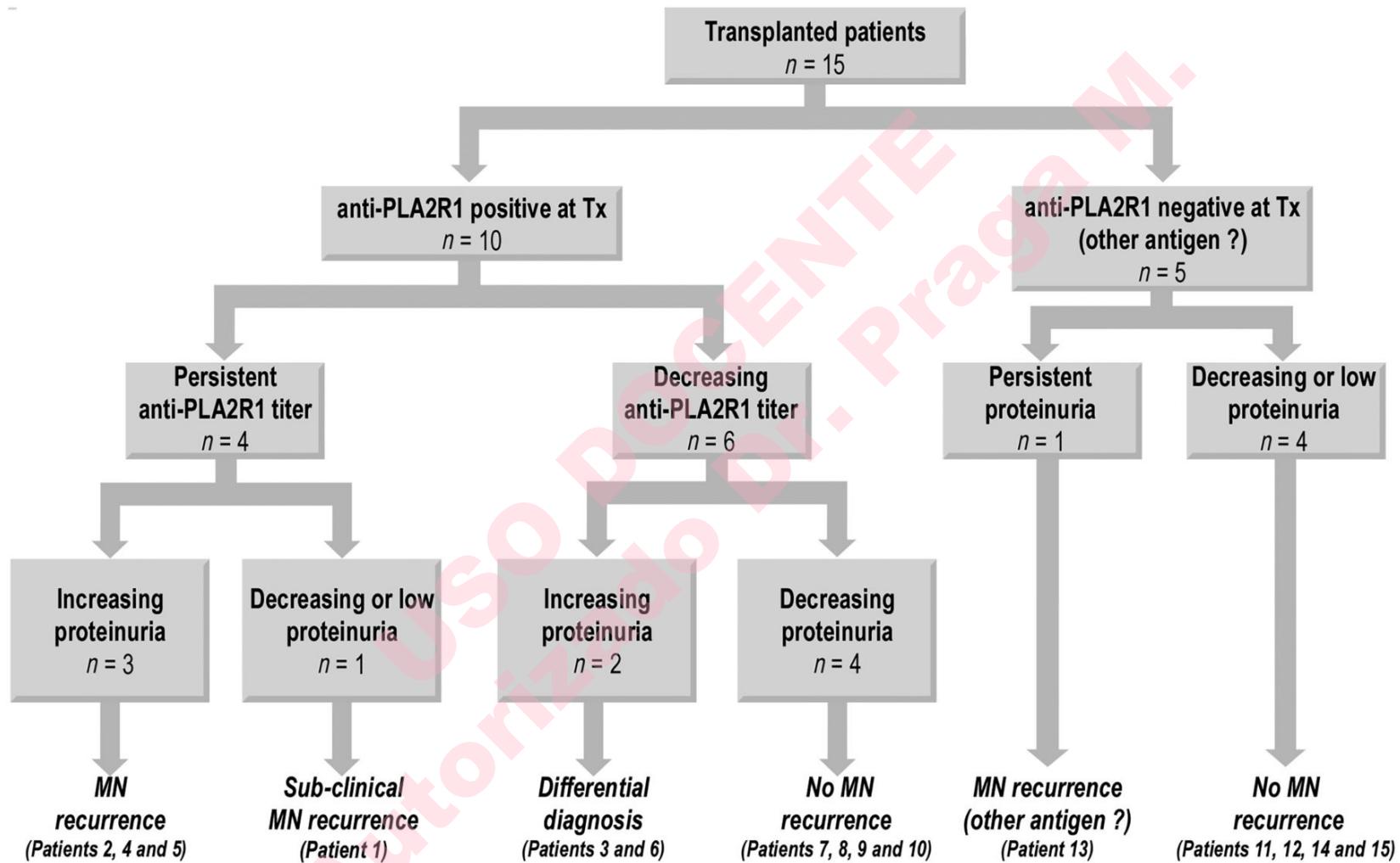
El-Zoghby, AJT 2009

Proportion of patients with recurrent MN



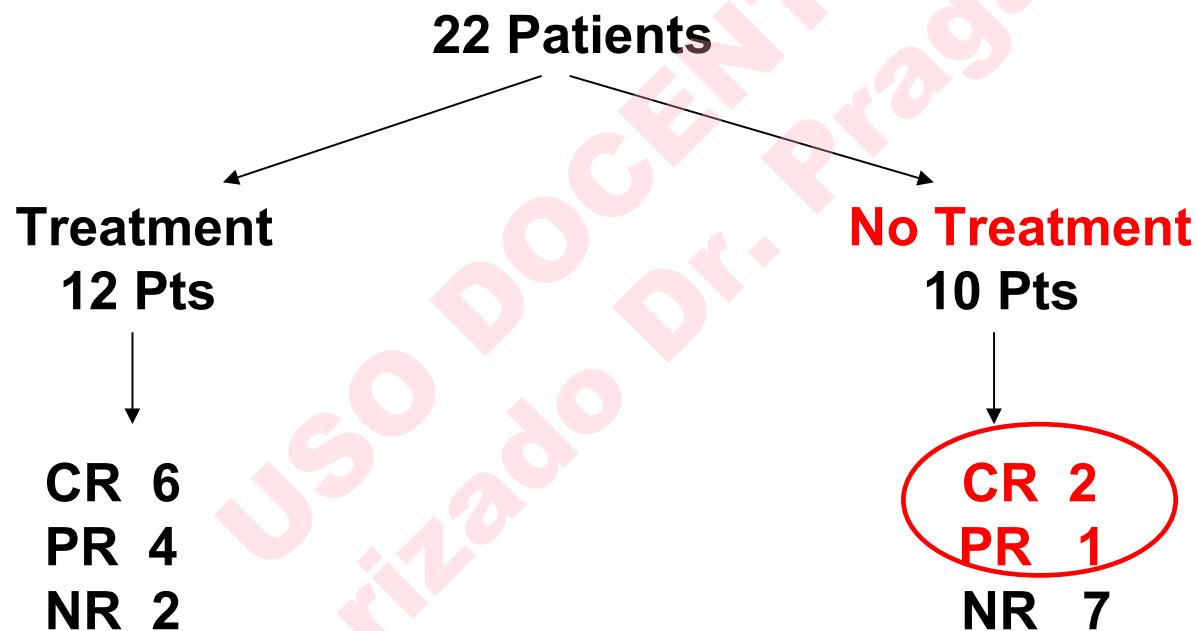
Recurrent Idiopathic Membranous Nephropathy After
Kidney Transplantation:
A Surveillance Biopsy Study
T. S. Dabade, Am J Transplant 2008

Working diagnostic tree using IgG4 anti-PLA2R1 activity at the time of renal transplantation and during follow-up, and proteinuria changes after renal transplantation.

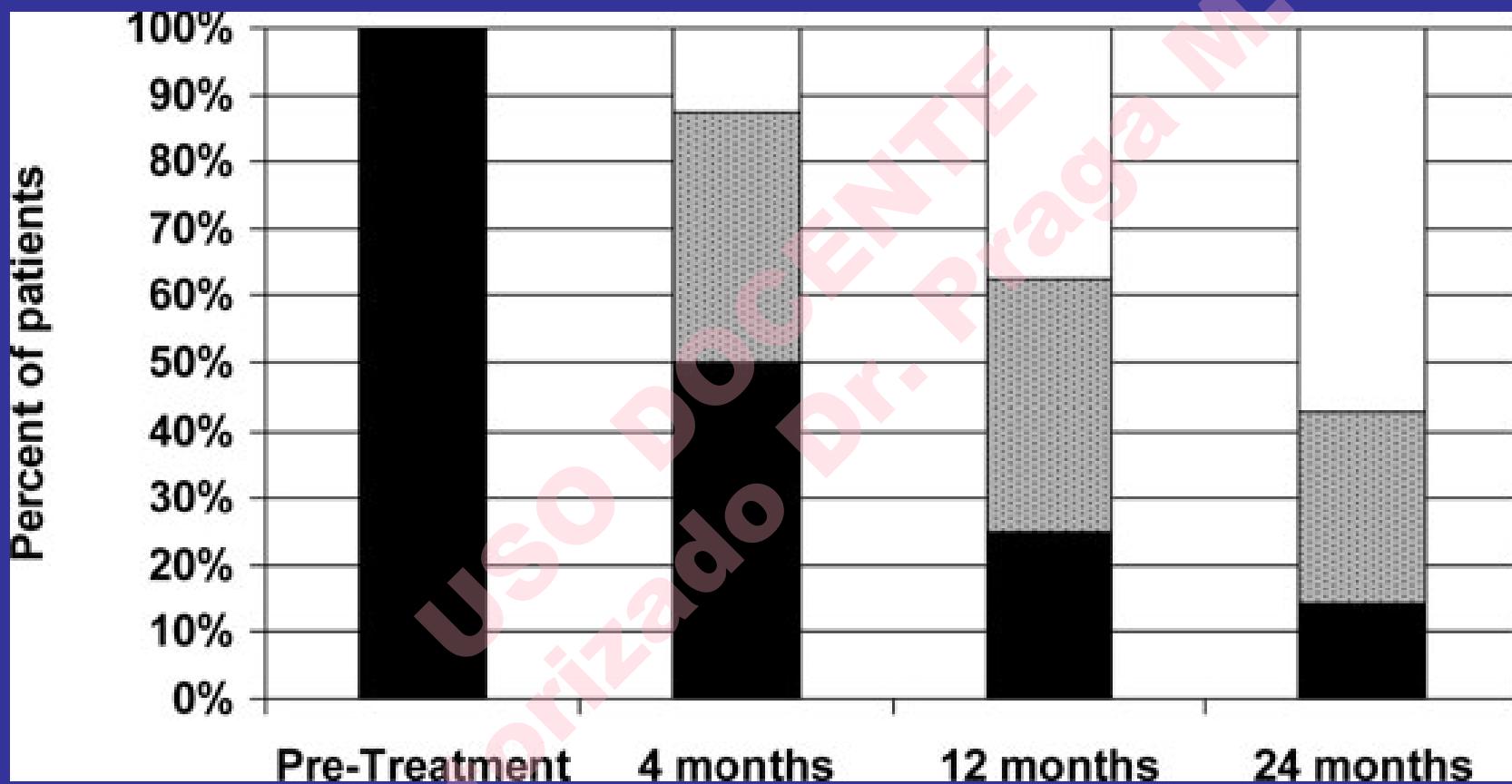


Barbara Seitz-Polski et al. *Nephrol. Dial. Transplant.*
2014;29:2334-2342

SPONTANEOUS REMISSION (SR) OF NEPHROTIC SYNDROME IN RECURRENT OR DE NOVO MEMBRANOUS NEPHROPATHY AFTER RENAL TRANSPLANTATION



Rituximab in Recurrent Idiopathic Membranous Nephropathy. El-Zoghby Z et al, Am J Transplant 2009



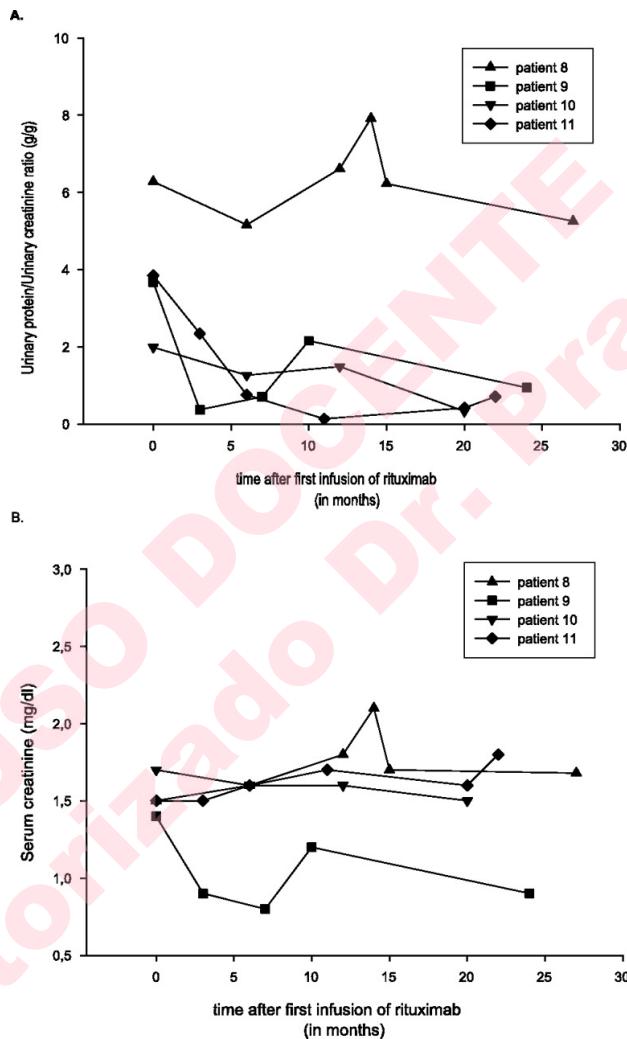
Percent of patients who achieved a complete remission (CR; open bar), partial remission (PR; grey bar) or no remission (NR; black)

Idiopathic Membranous Nephropathy

Different treatments for Different presentations

- 1. Initial Conservative Management** for all the patients (except those of Point 2), with a close monitoring, because of the possibility of Spontaneous Remission (30%)
- 2. Patients with Aggressive presentations** (Deteriorating renal function and massive nephrotic syndrome) (15-20%): **Ponticelli's regimen**
- 3. Persistence of nephrotic syndrome > 6-12 months without renal function worsening** (50-55%): **Ponticelli's regimen, Tacrolimus, Tacrolimus+Rituximab, Rituximab, ACTH**
- 4. Recurrence of MN in Renal Transplantation:** **Rituximab**
- 5. Usefulness of Anti-PLA2R Monitoring for the clinical management of the disease**

Effect of rituximab treatment on the urine protein/urine creatinine ratio (A) and serum creatinine (B).



Sprangers B et al. CJASN 2010;5:790-797

Membranous Nephropathy

Therapeutic Strategy (I)

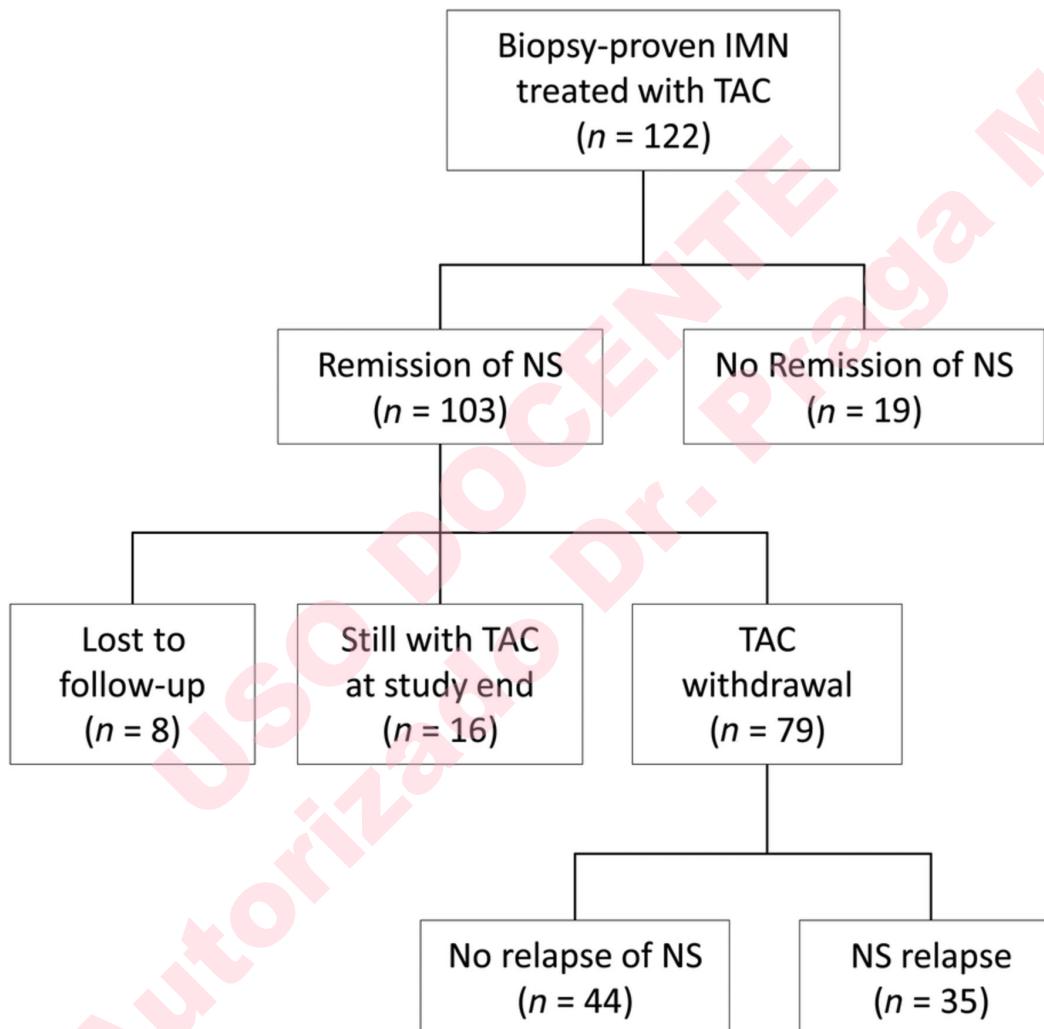
Conservative Management,
(including ACEI/ARB),
Close Monitoring

Possibility of Spontaneous Remission
(30%) (Polanco et al, JASN 2010)

Aggressive presentation:
Deteriorating renal function
massive nephrotic syndrome:
Steroids+alkylating agents
(15-20%)

Persistence of NS for > 6-12 months,
without tendency
to proteinuria decrease
and GFR>60 ml/m:
Tacrolimus for 6-9 months,
tapering off
for another 6-9 months
(50-55%)

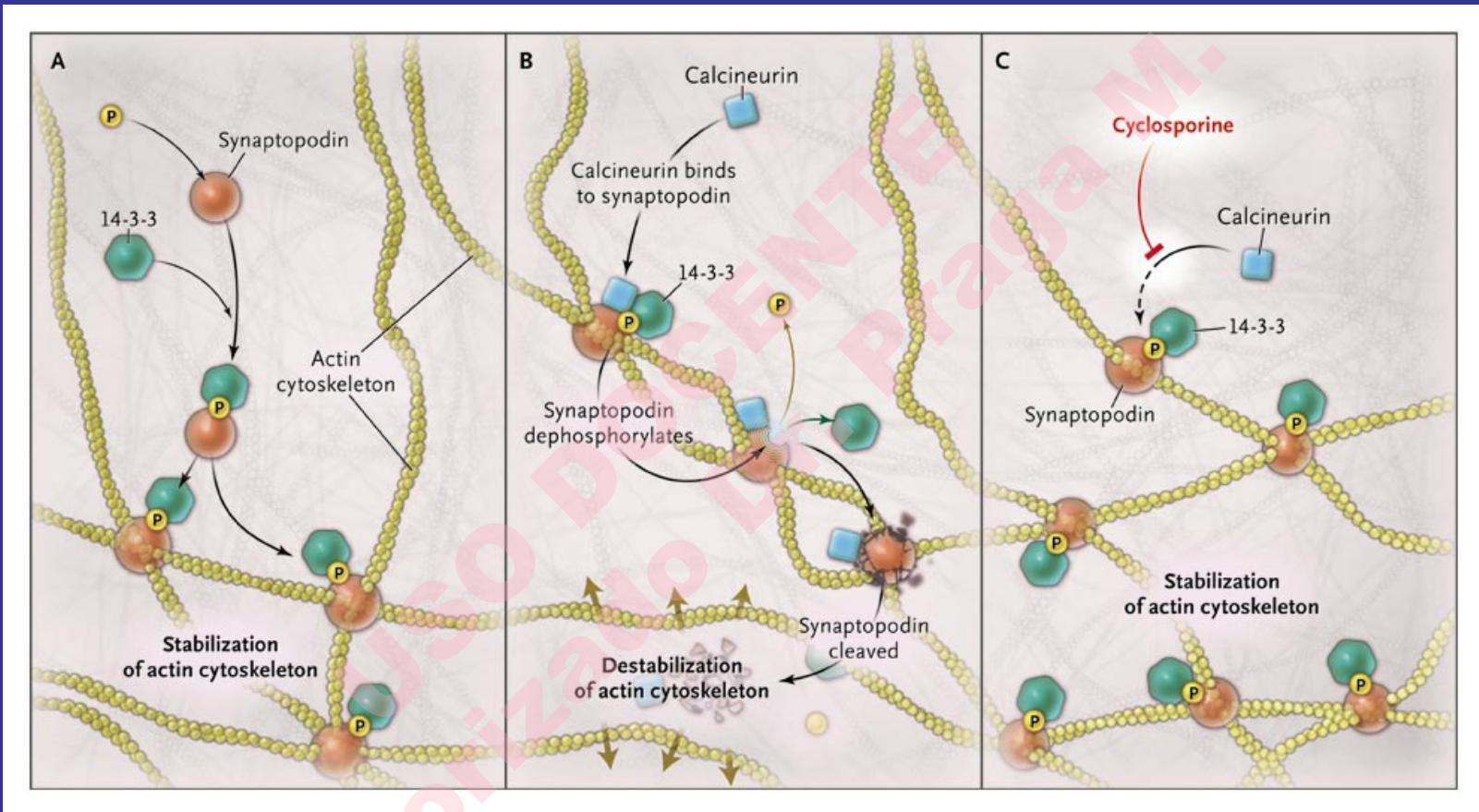
Patient flowchart.



Jara Caro et al. Nephrol. Dial. Transplant. 2014;ndt.gfu306

THE

The Effect of Calcineurin on Synaptopodin



Mathieson P. N Engl J Med 2008;359:2492-2494

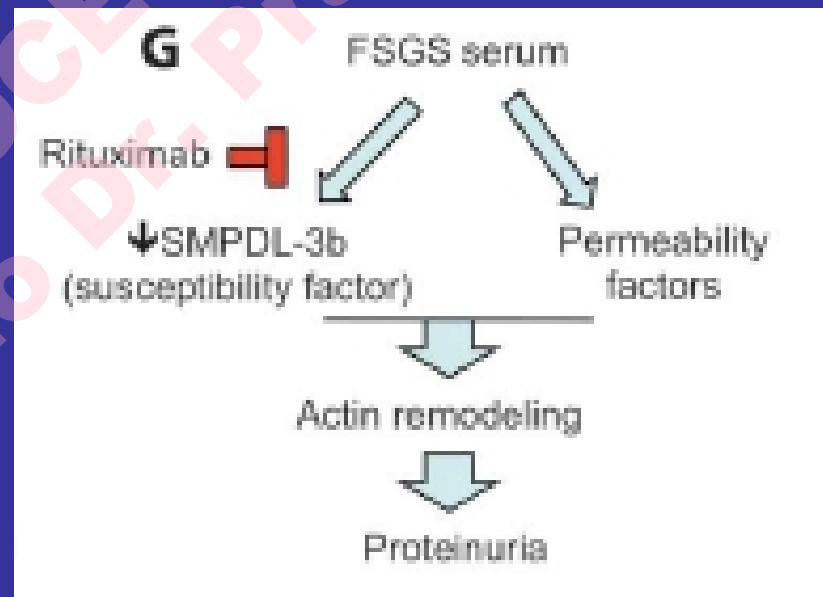
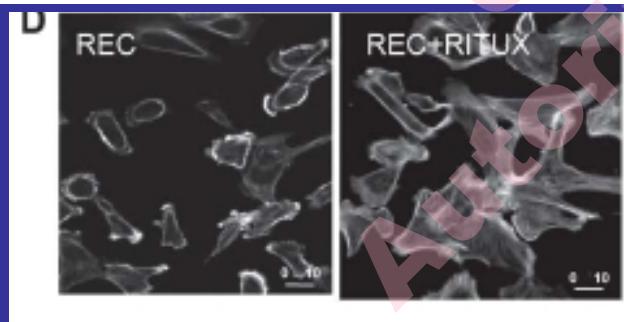
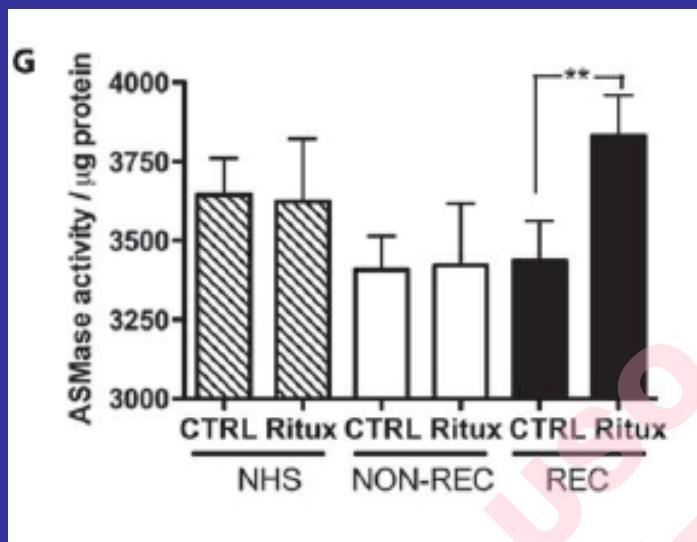
*The actin cytoskeleton of kidney podocytes
is a direct target of the antiproteinuric effect
of cyclosporine A*
Faul C et al Nat Med 2008



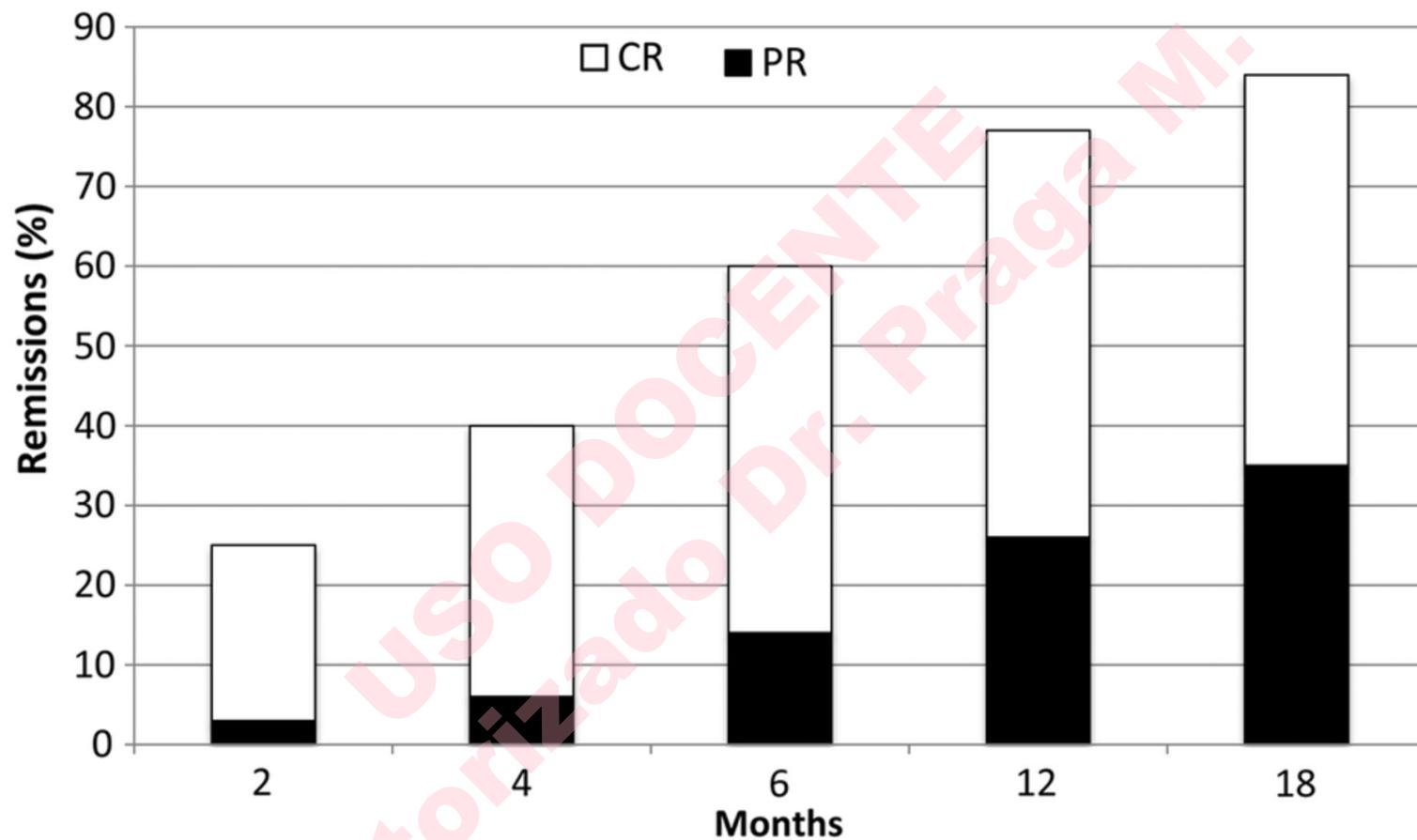
The NEW ENGLAND
JOURNAL of MEDICINE

Direct effects of Rituximab on podocytes

Science Translational Medicine 2011

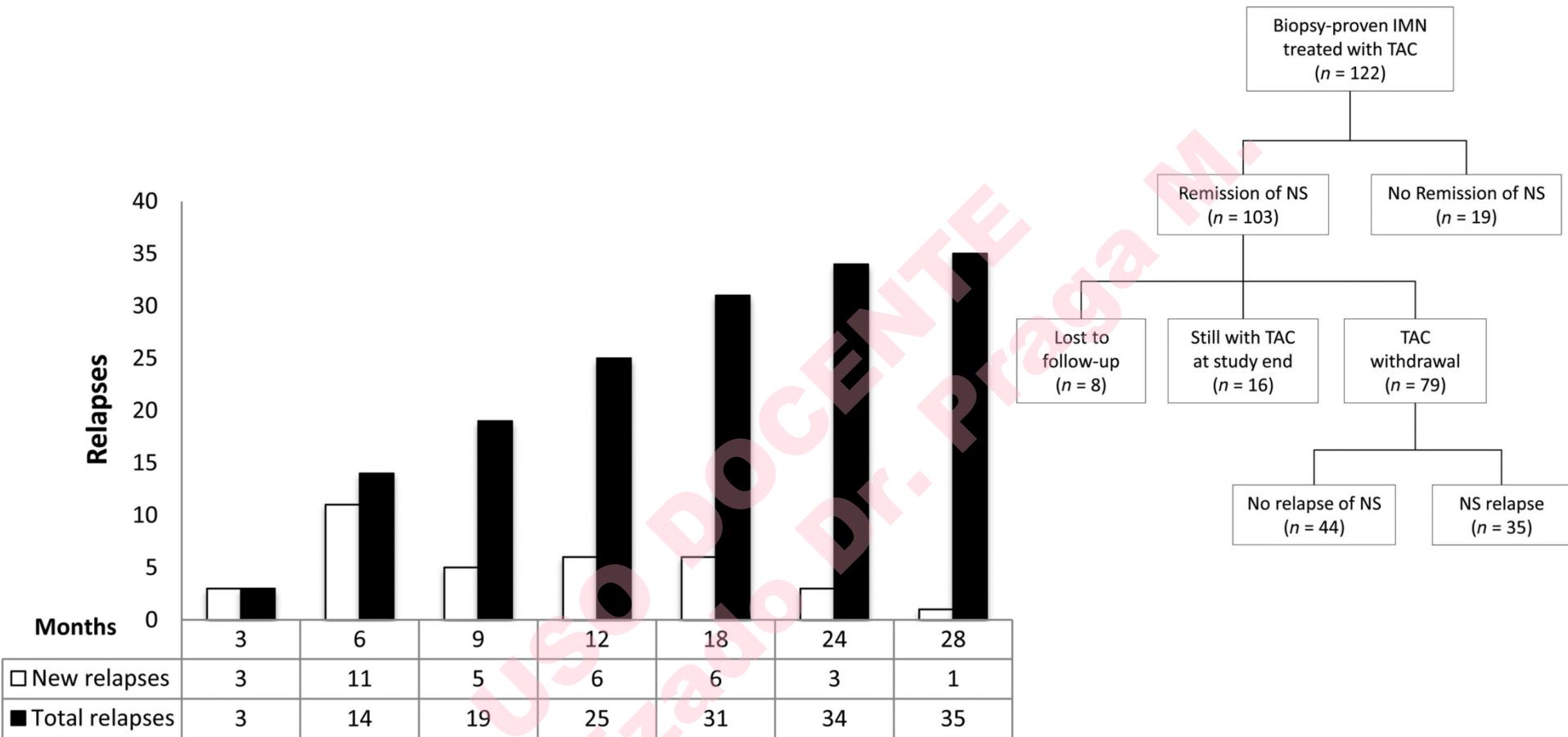


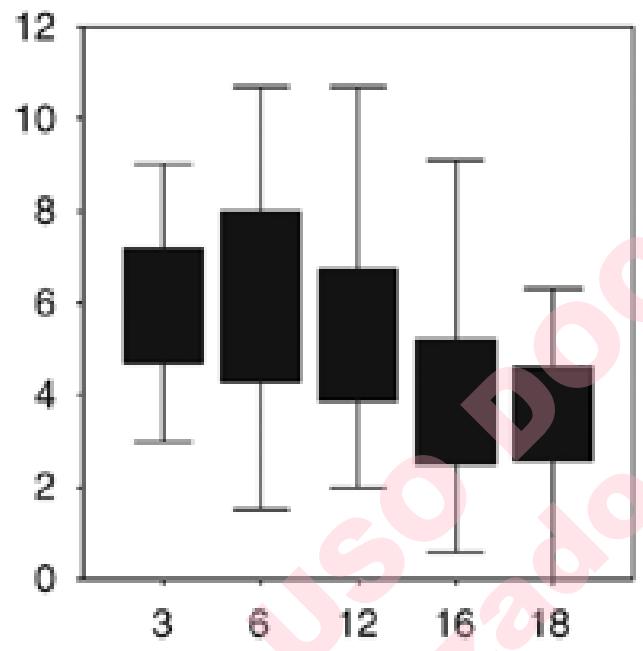
Percentage of complete (black) and partial (white) remissions after the onset of tacrolimus treatment.



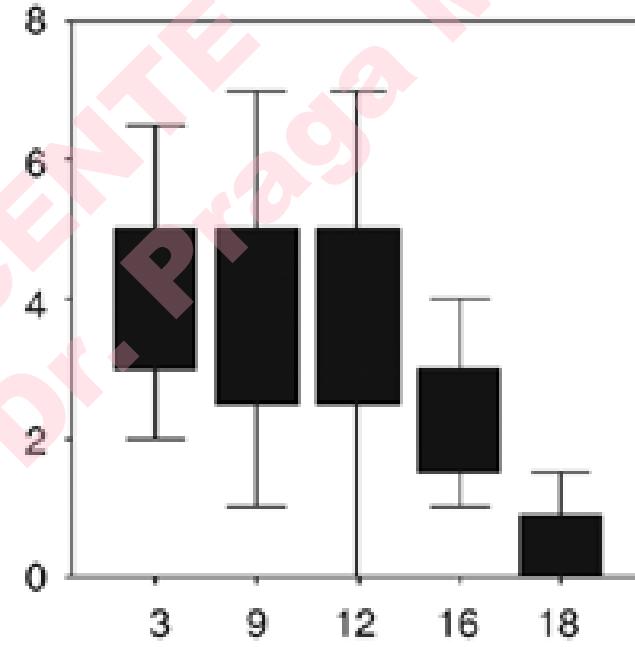
Jara Caro et al. Nephrol. Dial. Transplant. 2014;ndt.gfu306

Monthly incidence and cumulative number of relapses after the onset of tacrolimus tapering.





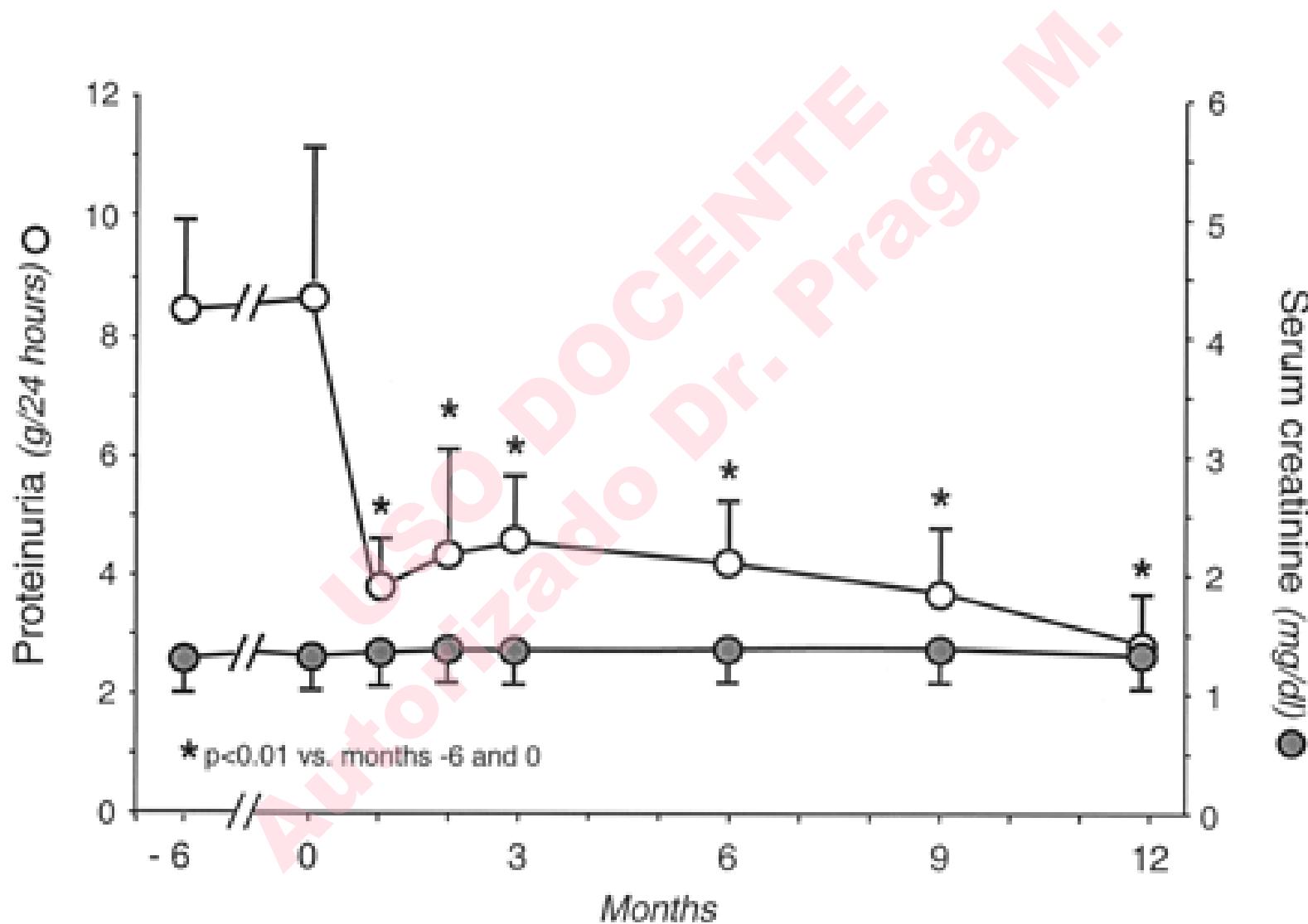
Mean doses of tacrolimus (mg/day)



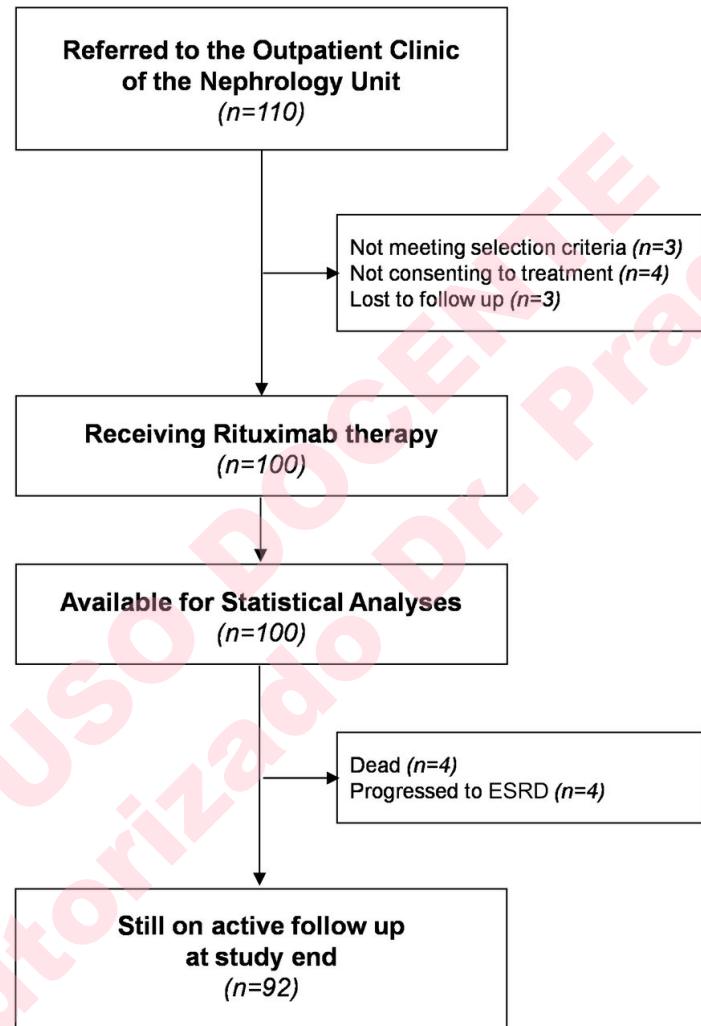
Mean blood levels of tacrolimus (ng/ml)

Effect of Immunosuppressive Treatments on PLA2R1

USO DOCENTE
Autorizado Dr. Praga M.

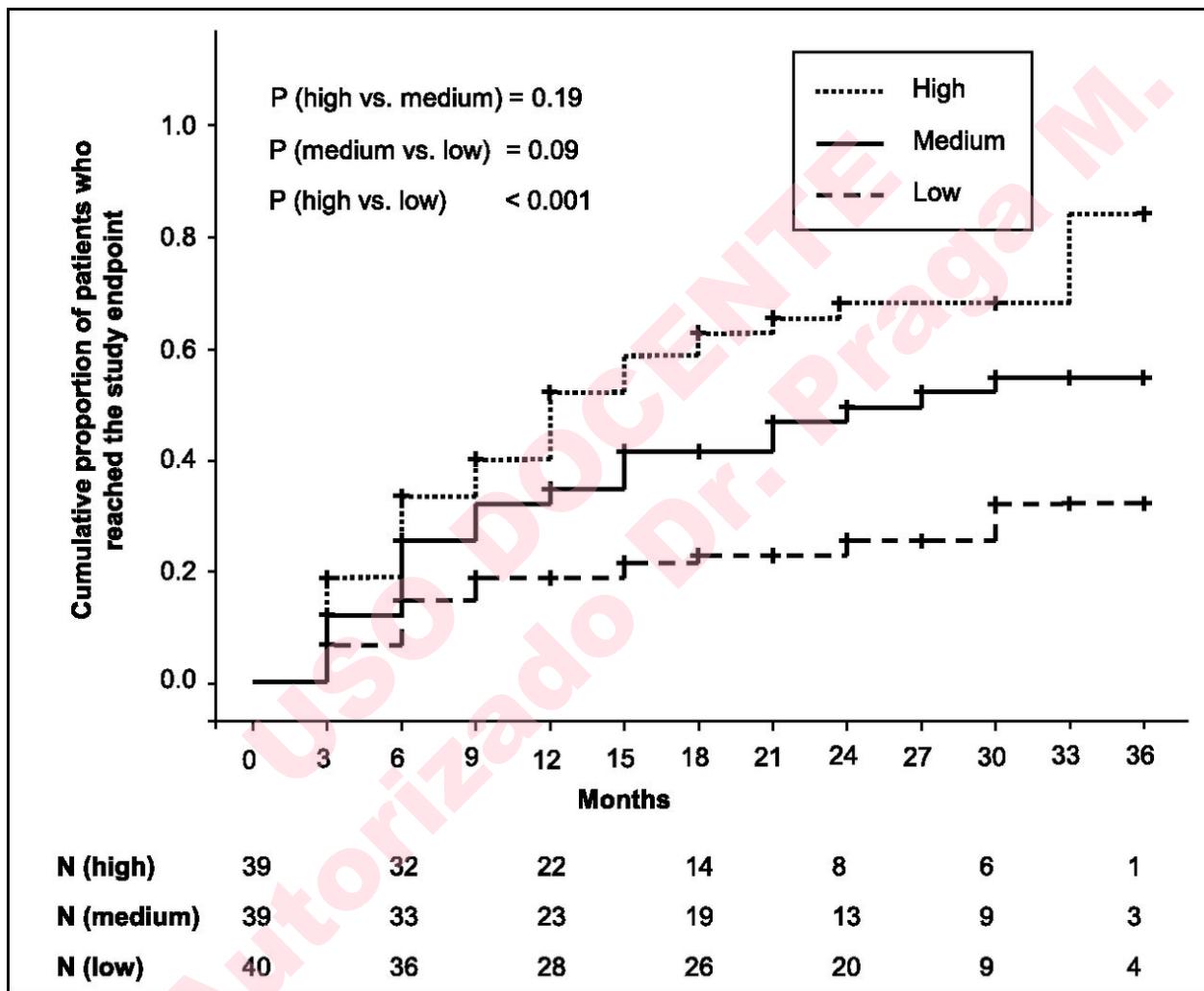


Patient flow chart.



Piero Ruggenenti et al. JASN 2012;23:1416-1425

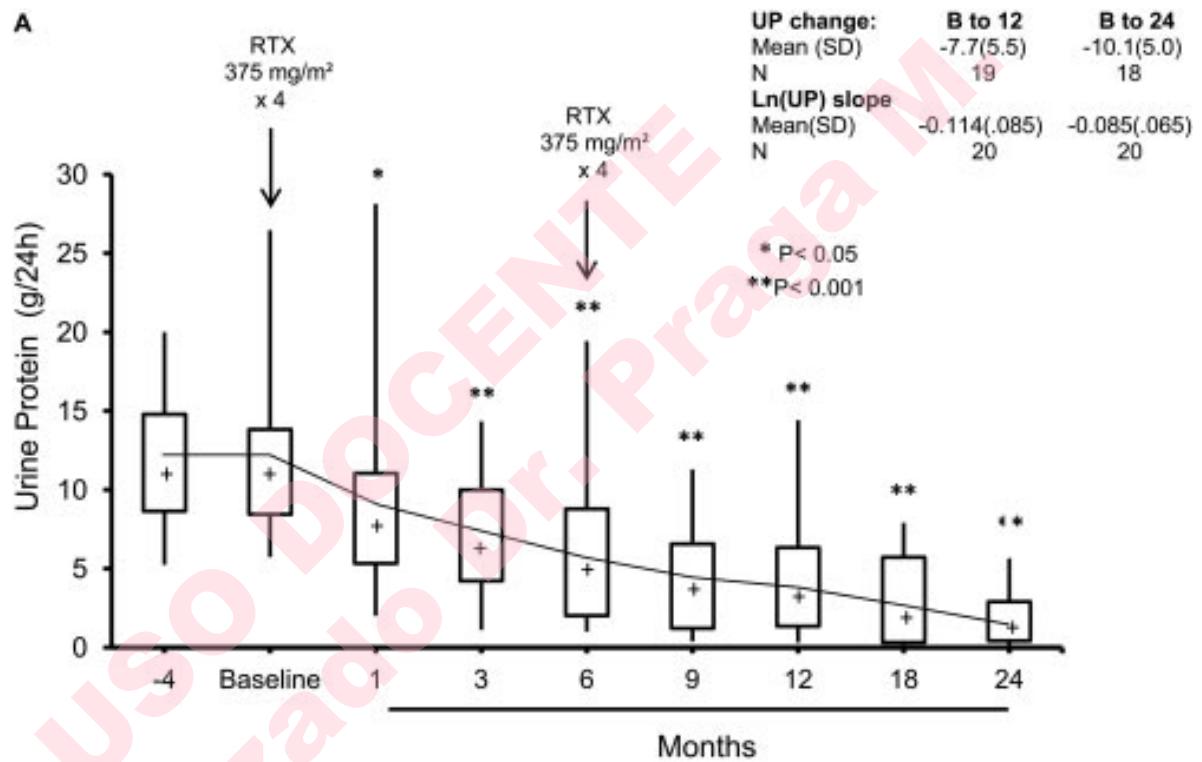
Survival analysis by M-type PLA2R-Ab-level tertile.



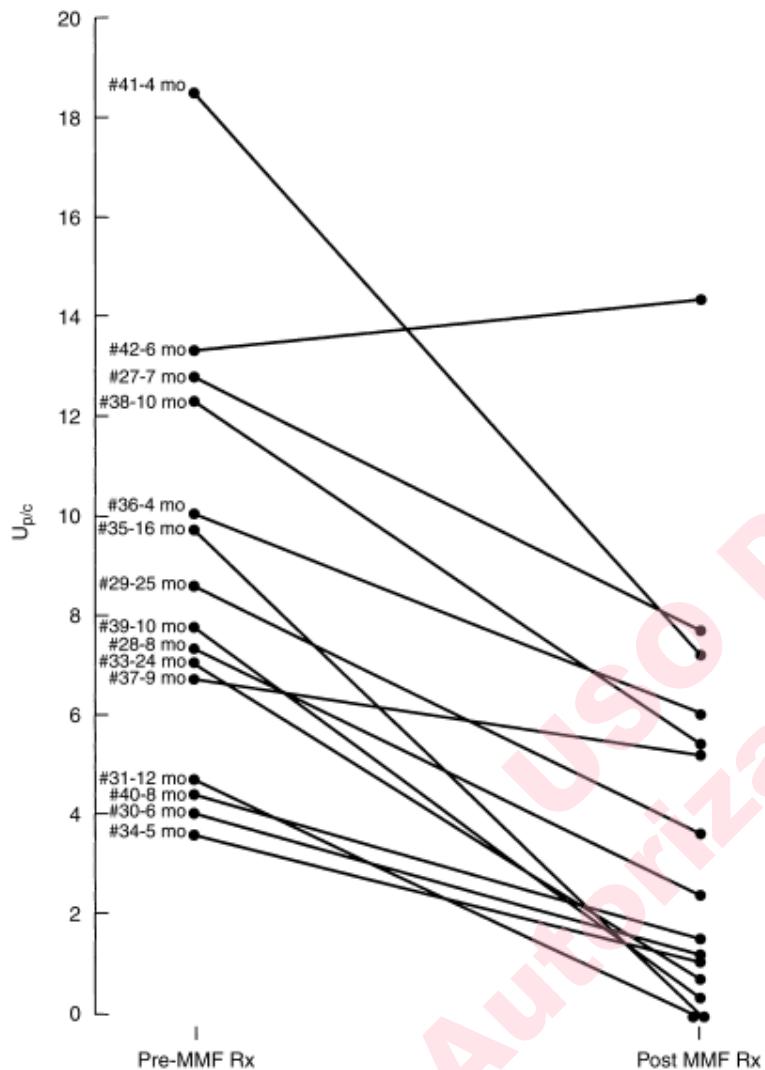
Elion Hoxha et al. CJASN 2014;9:1883-1890

CJASN

**18/20 in remission
at 24 mo.**



**Choi et al: Mycophenolate Mofetil treatment for primary glomerular diseases
KI 2002**



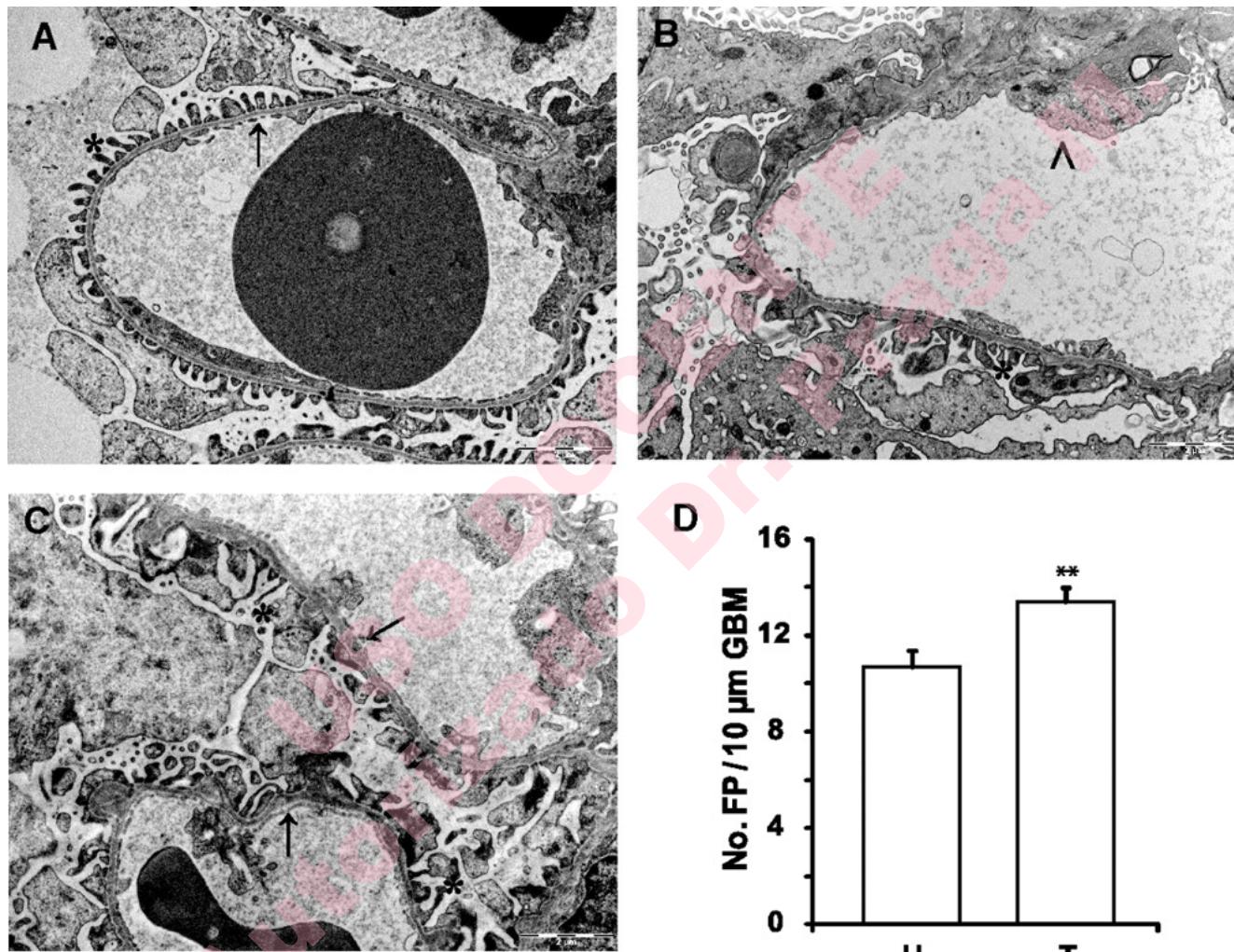
**Segarra A, et al. Efficacy and safety of “rescue therapy” with mycophenolate mofetil in resistant primary GN.
NDT 2007**

21 pts with IMN and proteinuria > 3.5 g/d despite ACEI, Corticosteroids, CsA....
GFR <60 ml/min in 52%

MMF 1.5-2 g/día for 1 yr.
Baseline Proteinuria 7.9 ± 2.1 g/d
1-yr Proteinuria 3.1 ± 1.4 g/d

Complete Remission 0%
Partial Remission 52%
Stable renal function

Melanocortin receptor agonist treatment improves glomerular morphology in PHN rats.



Lindskog A et al. JASN 2010;21:1290-1298

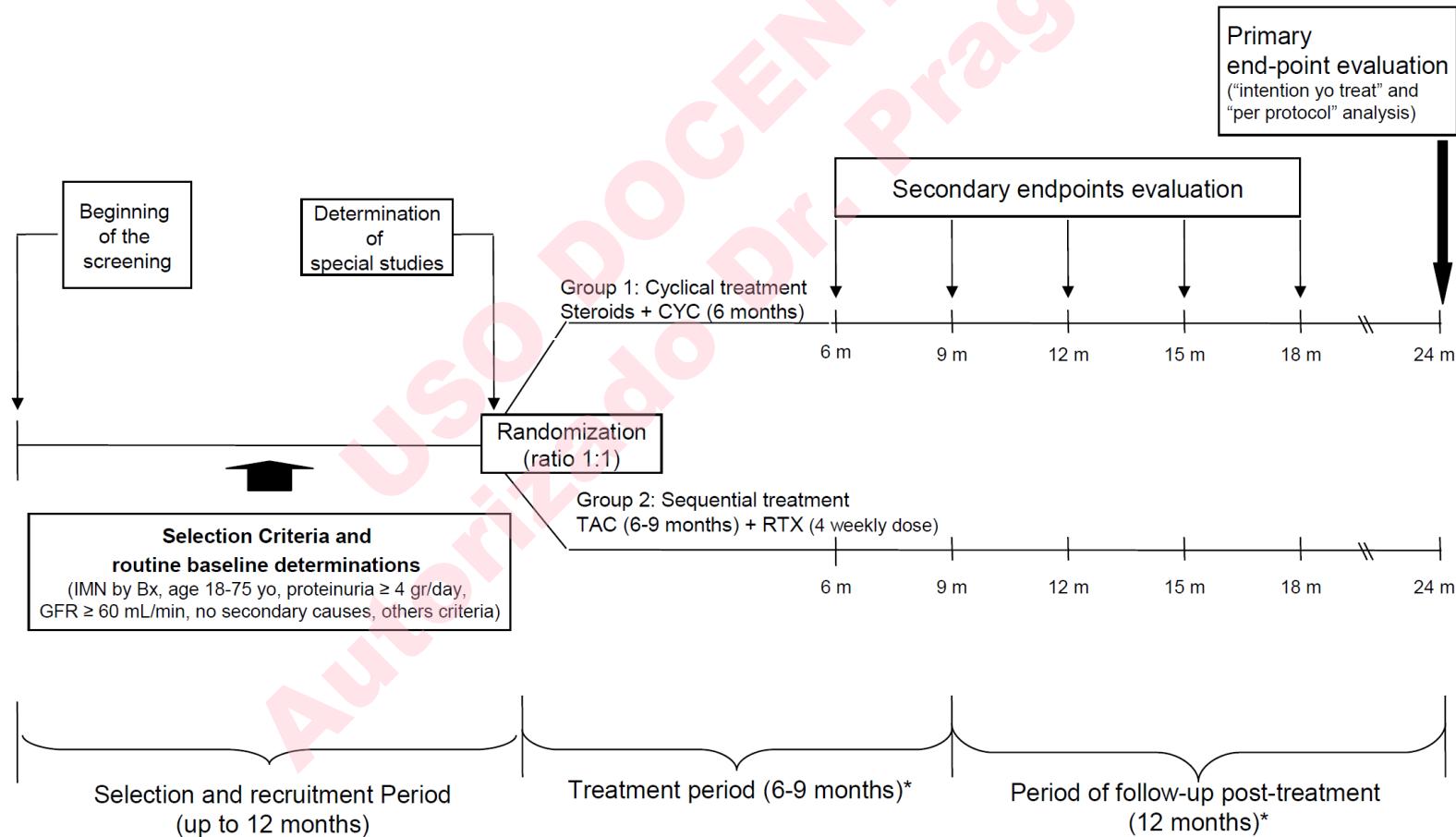
JASN

Influence of residual proteinuria on renal outcomes in IgAN and MN

IgAN (n=85)	< 1 g (51)	> 1 g (34)	p
> 50% Scr increase	5.9%	50%	<0.0001
>100% Scr increase	2%	47.1%	<0.0001
ESRD	2%	41.2%	<0.0001

Proteinuria Target for IgAN - <0.5-1 g/day

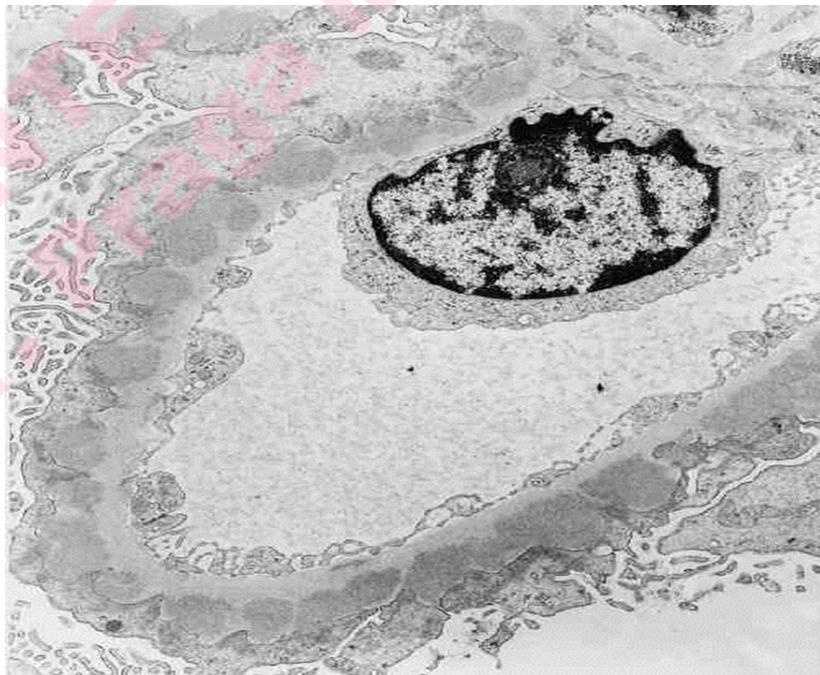
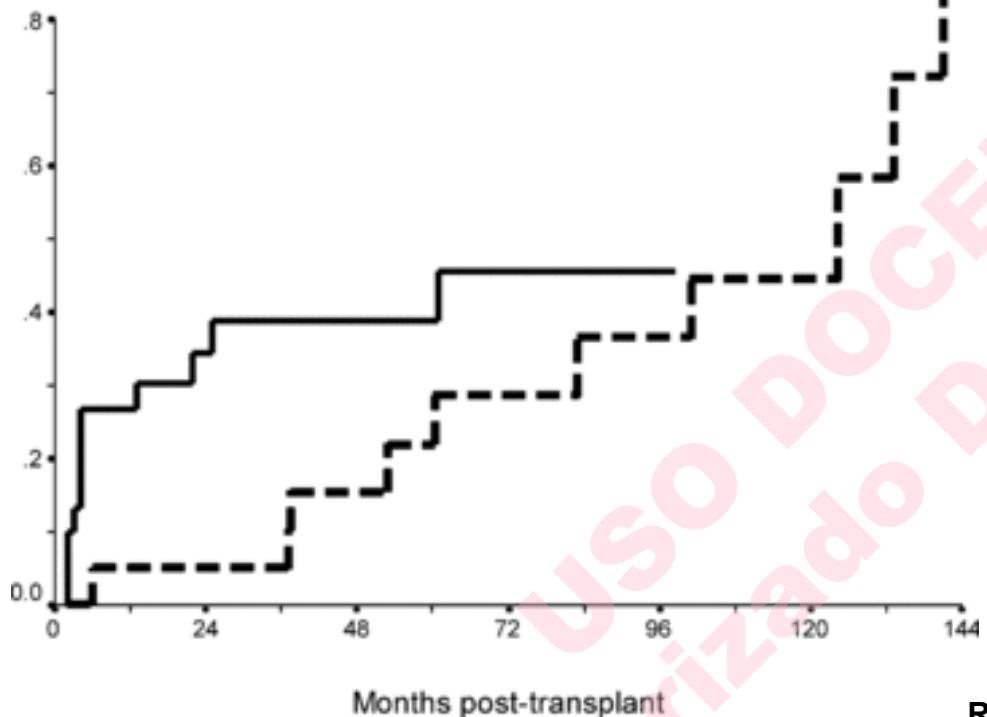
Membranous Nephropathy (n=129)	< 1 g (84)	> 1 g (45)	p
> 50% Scr increase	6%	8.9%	0.42
>100% Scr increase	2.4%	2.2%	0.58
ESRD	0	0	



Recurrent Idiopathic Membranous Nephropathy: Early Diagnosis by Protocol Biopsies and Treatment with Anti-CD20 Monoclonal Antibodies

El-Zoghby, AJT 2009

Proportion of patients with recurrent MN



Recurrent Idiopathic Membranous Nephropathy After
Kidney Transplantation:
A Surveillance Biopsy Study
T. S. Dabade, Am J Transplant 2008

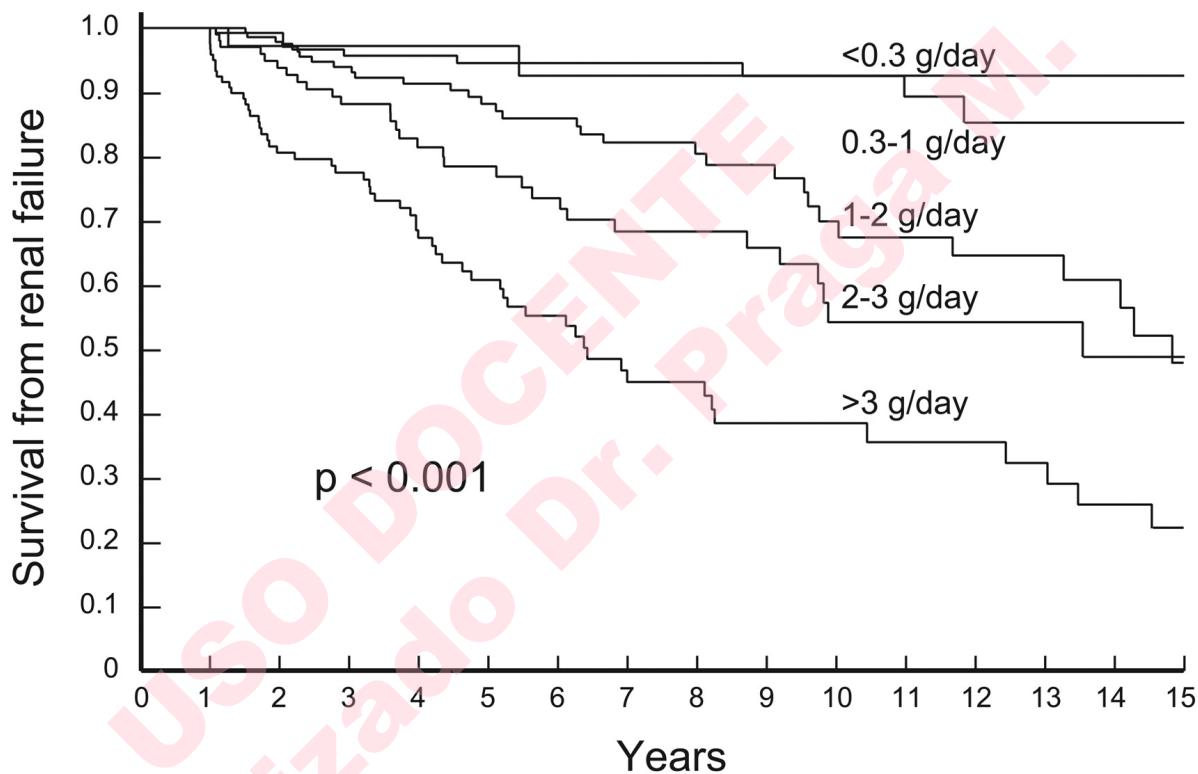
Sequential Therapy TAC- RTX to prevent relapses in IMN

Baseline (at RTX treatment) characteristics.

Pac	Age	Gender	Time Tac/CsA	Tac/CsA dose	Tac/CsA trough level	SBP	DBP	sCr	GFR	Alb	Prot
1	26	M	44	4	5,6	124	65	1,26	98	4,1	2,90
2	32	M	51	4	7,0	123	54	1,34	100	4,0	2,60
3	54	F	22	3	8,1	132	57	1,40	97	3,8	1,90
4	31	M	28	4	7,1	125	68	,98	101	4,0	2,20
5	42	M	36	4	6,9	118	79	,87	97	4,1	3,20
6	54	M	29	4	7,1	119	65	1,44	95	4,2	2,60
7	62	F	51	3	8,2	124	67	,89	131	4,0	3,10
8	71	M	54	4	5,7	125	72	1,45	80	4,4	3,18
9	55	M	47	3,5*	198*	125	78	1,25	84	3,97	2,29
10	45	M	80	4	7,7	114	69	1	80	3,8	0,7
11	49	M	83	4	9	115	75	0,98	94	4,2	2,7
12	38	M	21	3,6*	150*	106	65	0,85	115	3,8	1,85
13	42	M	24	3,7*	175*	115	57	1,03	113	4,1	1,77

Segarra et al, Clin JASN 2009

Reich, H. N. et al. J Am Soc Nephrol 2007;18:3177-3183
Renal survival by category of TA-proteinuria



JASN™

TA-proteinuria category	n	Median survival (years)	5-year survival (%)	10-year survival (%)	15-year survival (%)
<0.3 g/day	37	22	8	1	
0.3-1 g/day	134	79	35	11	
1-2 g/day	145	79	28	10	
2-3 g/day	105	50	18	4	
>3 g/day	120	44	13	6	



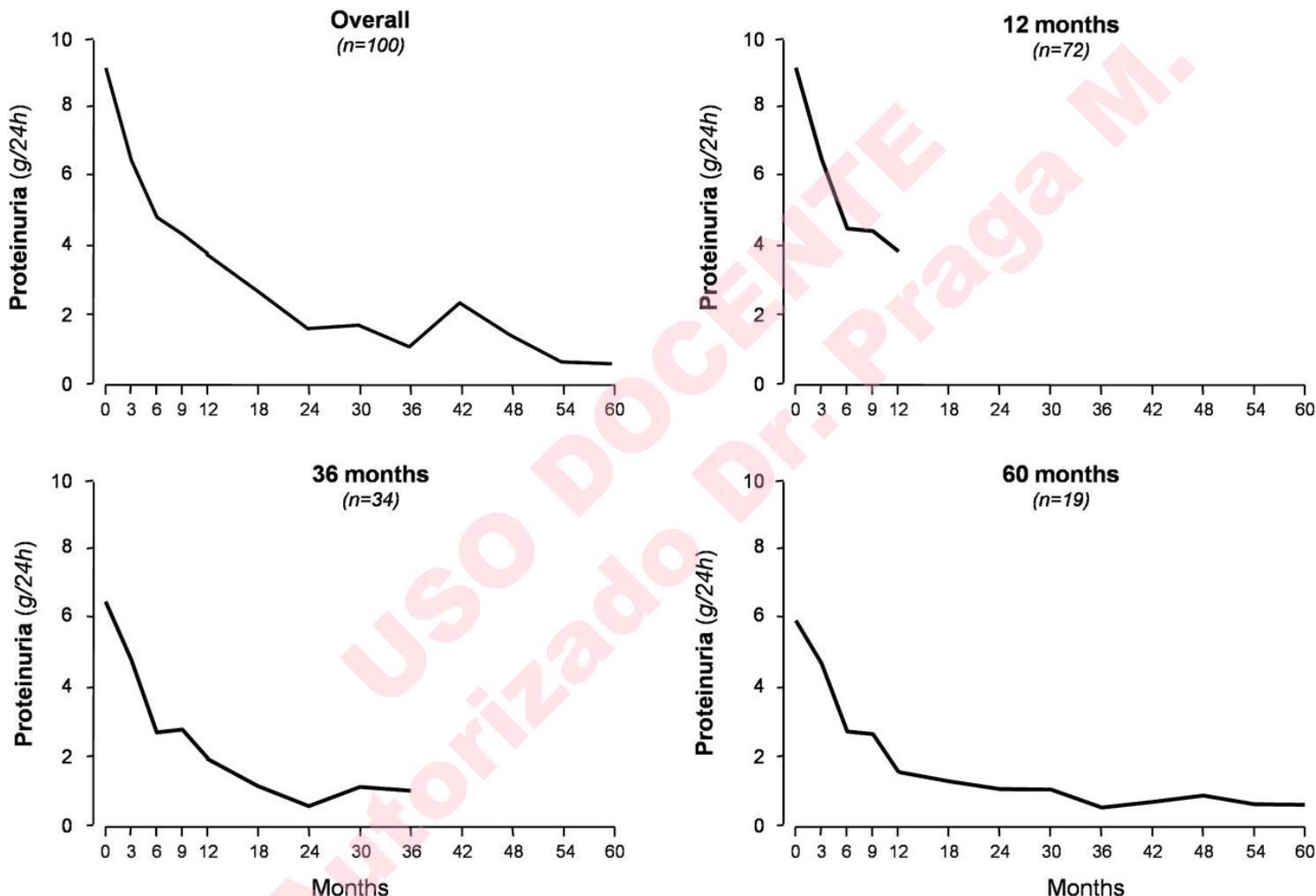
Membranous Nephropathy

7.2: Selection of patients with IMN to be considered for treatment with corticosteroids and immunosuppressive agents

7.2.1: We recommend that initial therapy be started **ONLY in patients with nephrotic syndrome AND when at least ONE of the following conditions are met:**

- urinary protein excretion persistently exceeds 4 g/d, remains >50% of baseline value, **AND does not show progressive decline**, during antihypertensive and antiproteinuric therapy (see Chapter 1) during an observation period of at least 6 months. (1B)
- the presence of **severe, disabling or life-threatening symptoms related to the nephrotic syndrome**. (1C)
- **sCr has risen by 30% or more from the time of diagnosis over the time frame of 6-12 months, but eGFR is not less than 25-30 mL/min/1.73m² AND this change is not explained by superimposed complications.** (2C)

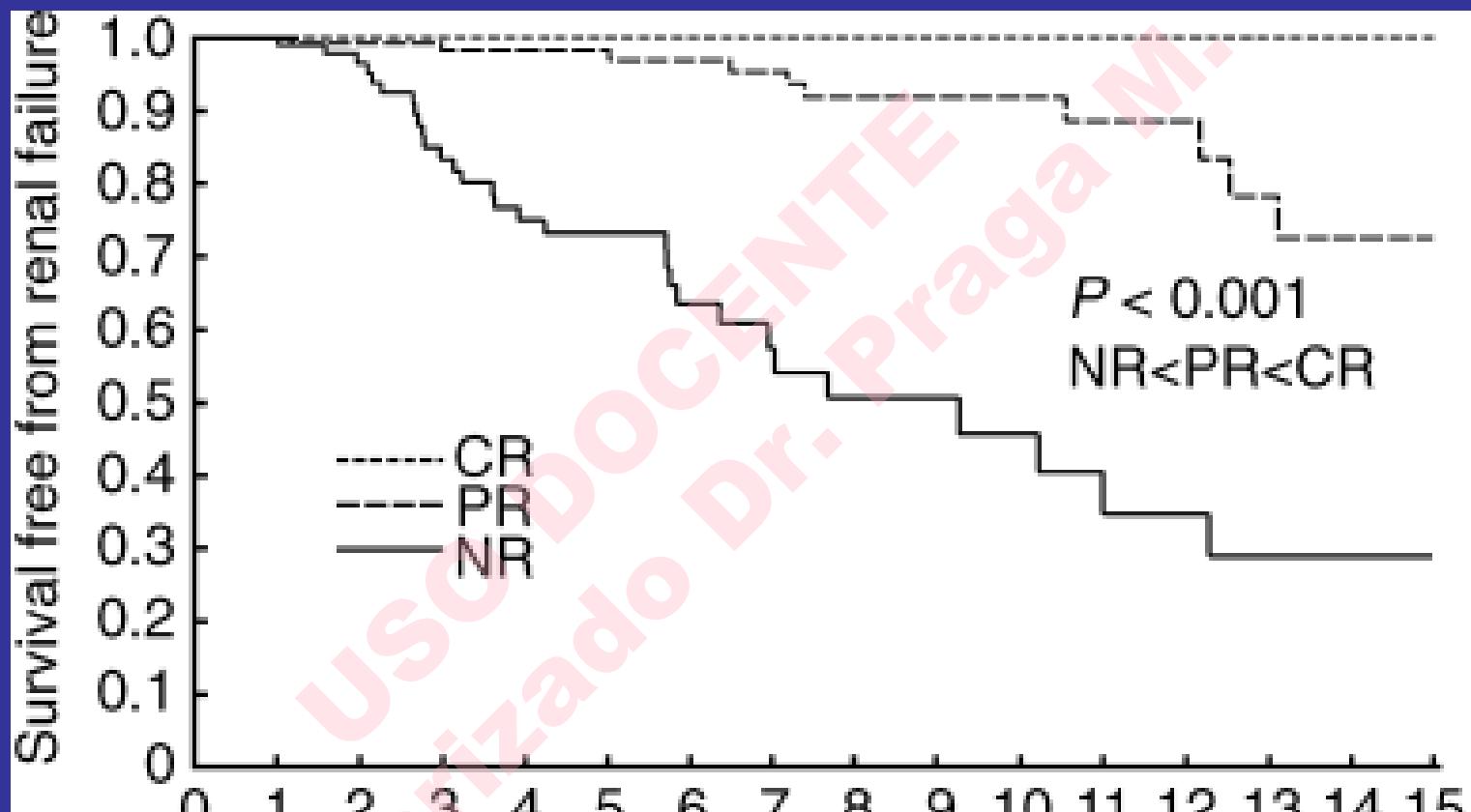
Median 24-hour urinary protein excretion at baseline (month 0), at 3, 6, 9, and 12 months and at 6-monthly evaluations after rituximab administration in the study group as a whole (overall) and in different cohorts with homogeneous follow-up durations.



Piero Ruggenenti et al. JASN 2012;23:1416-1425

JASN

Troyanov S et al: Idiopathic membranous nephropathy: definition
And relevance of a partial remission
Kidney Int 66: 1199-1205, 2004



CR	102	67	33	12
PR	135	74	32	9
NR	106	34	9	4

Membranous Nephropathy

Therapeutic Strategy

Conservative Management,
(including ACEI/ARB),
Close Monitoring

Possibility of Spontaneous Remission
(32%; *Polanco et al, JASN 2010*)

Anti-PLA2R Monitoring

Aggressive presentation:
Deteriorating renal function
massive nephrotic syndrome:
**Steroids+alkylating agents
(15-20%)**

Persistence of NS for > 6-12 months,
without tendency
to proteinuria decrease
and without deteriorating renal function
(50-55%)
Steroids+alkylating agents
Calcineurin inhibitors
Rituximab
ACTH

Membranous Nephropathy

Therapeutic Strategy

**Conservative Management,
(including ACEI/ARB),
Close Monitoring**

**Possibility of Spontaneous Remission
(32%; *Polanco et al, JASN 2010*)**

**Aggressive presentation:
Deteriorating renal function
massive nephrotic syndrome:**

(15-20%)

Membranous Nephropathy

Therapeutic Strategy

**Conservative Management,
(including ACEI/ARB),
Close Monitoring**

**Possibility of Spontaneous Remission
(32%; *Polanco et al, JASN 2010*)**

Aggressive presentation:
Deteriorating renal function
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Persistence of NS for > 6-12 months,
without tendency
to proteinuria decrease
and without deteriorating renal function
(50-55%)

Spontaneous remission of nephrotic syndrome in membranous nephropathy with chronic renal impairment

Polanco N et al, GLOSEN

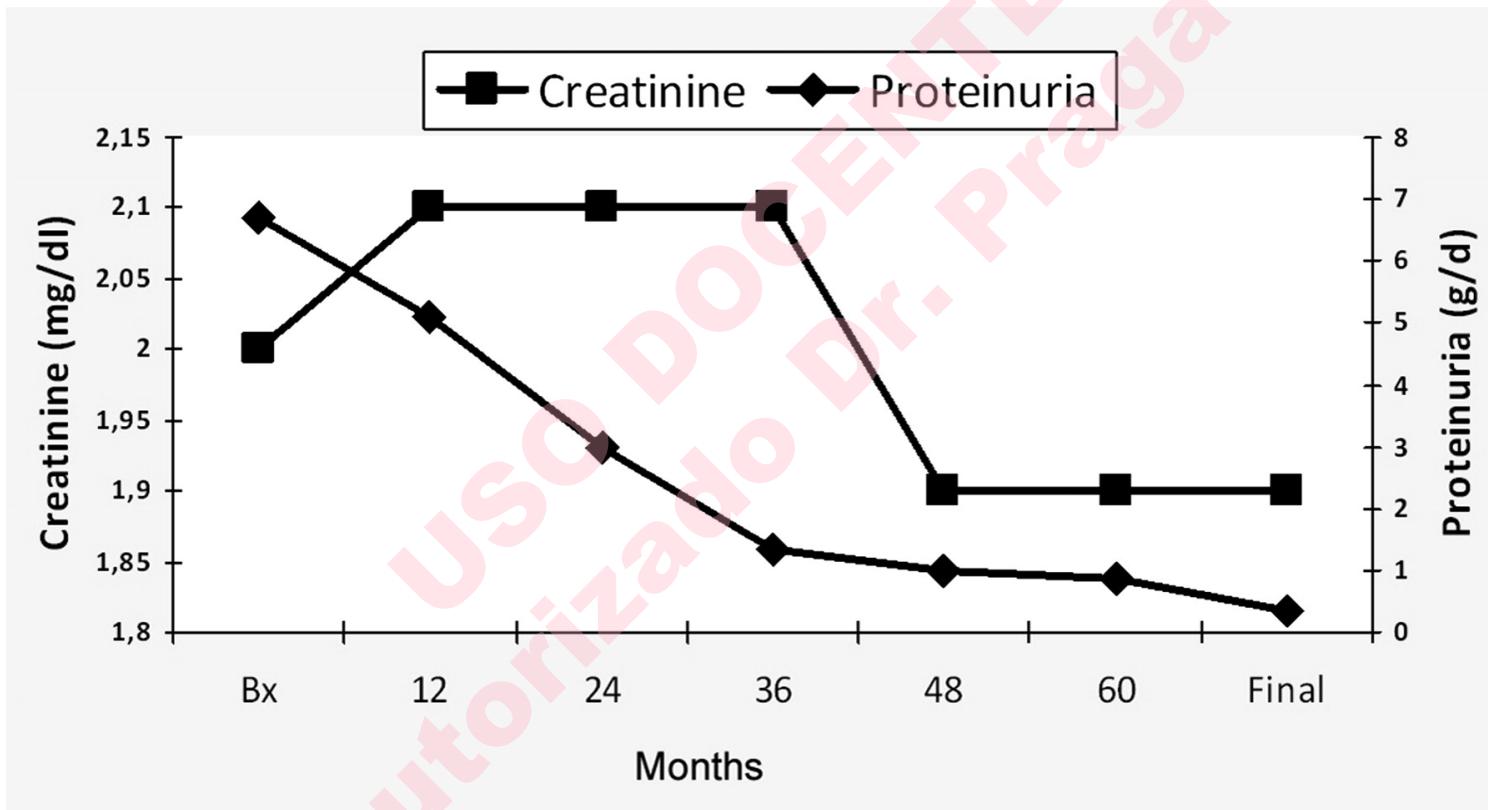
Table 1. Demographic and clinical characteristics^a

Patient	Age ^b /gender	SCr (mg/dL) ^b	CrCl (mL/m)	P (g/day) ^b	RAS blockade	Peak SCr (mg/dL)	Time to peak SCr (months)	Time to SR (months)	Relapse	Final SCr (mg/dL)	Final P (g/day)	Follow-up (months)
1	47/M	1.9	57	6.8	No	2.2	4	48	No	1.4	0.6	120
2	51/M	1.4	67	5.6	Yes	2.1	24	30	No	1.7	0.2	72
3	69/F	1.4	43	8.4	Yes	1.9	12	20	No	1.47	0	228
4	56/M	2.1	47	3.52	Yes	2.3	42	30	No	2.3	0	225
5	66/F	1.7		14.4	Yes	2.6	24	30	Yes	6.7 ^c	5.4	132
6	52/M	1.5	68	15	Yes	1.9	10	16	No	1.3	0	180
7	55/M	4.3	18	5.6	Yes	6.5	4	12	Yes	6.1 ^c	3.3	120
8	69/M	3.4	19	9	Yes	4.1	12	12	No	3.9	1	118
9	56/F	1.4	68	7.6	Yes	2	30	36	No	2	0.3	183
10	77/M	1.4	42	5.4	Yes	1.7	60	66	No	1.6	0.5	106
11	71/M	2.3	29	6.6	Yes	2.8	36	6	No	2.6	0.2	60

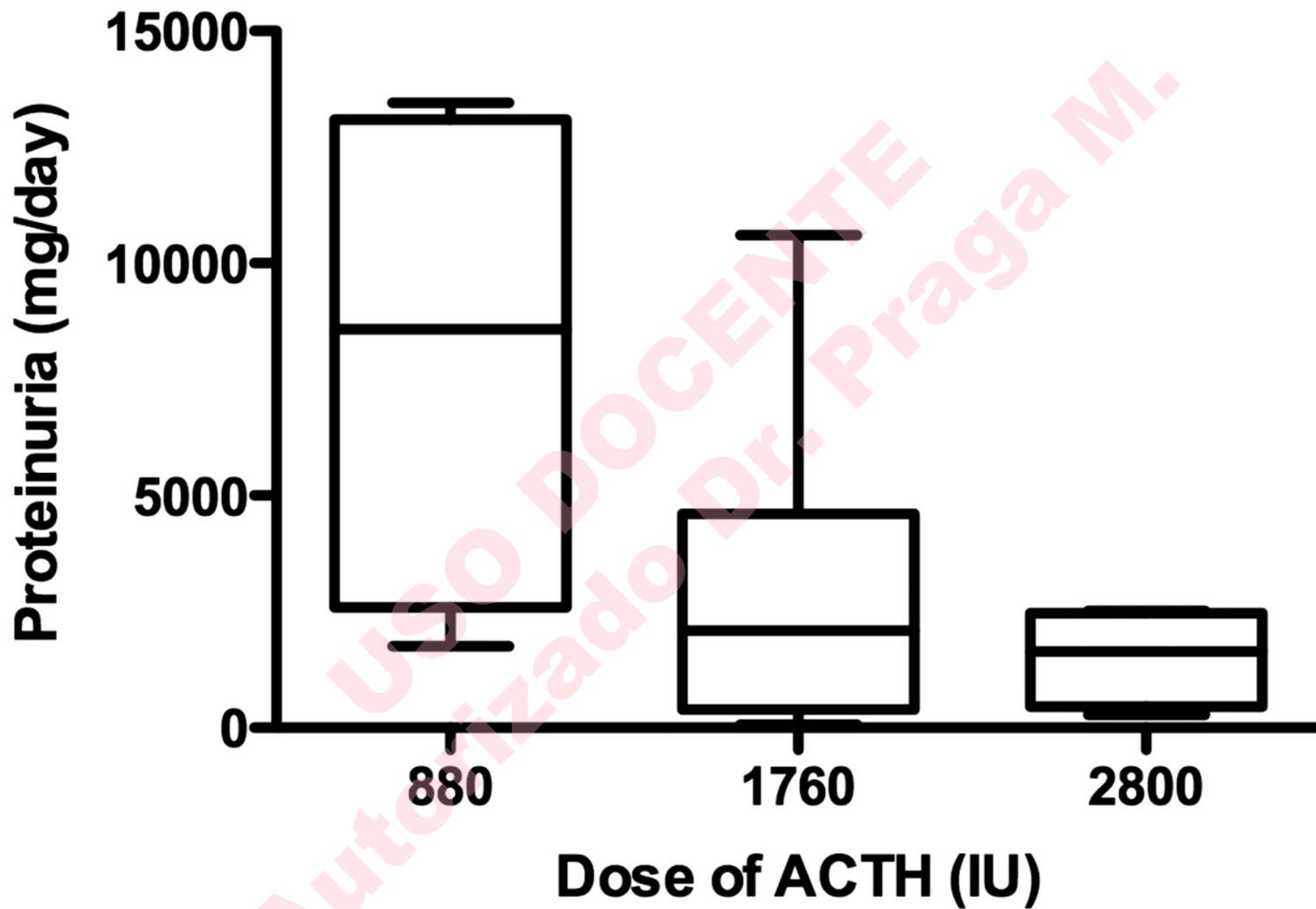
Spontaneous Remission of nephrotic syndrome in membranous nephropathy with chronic renal impairment

Polanco et al; GLOSEN. NDT 2011

Evolution of mean Scr and proteinuria.

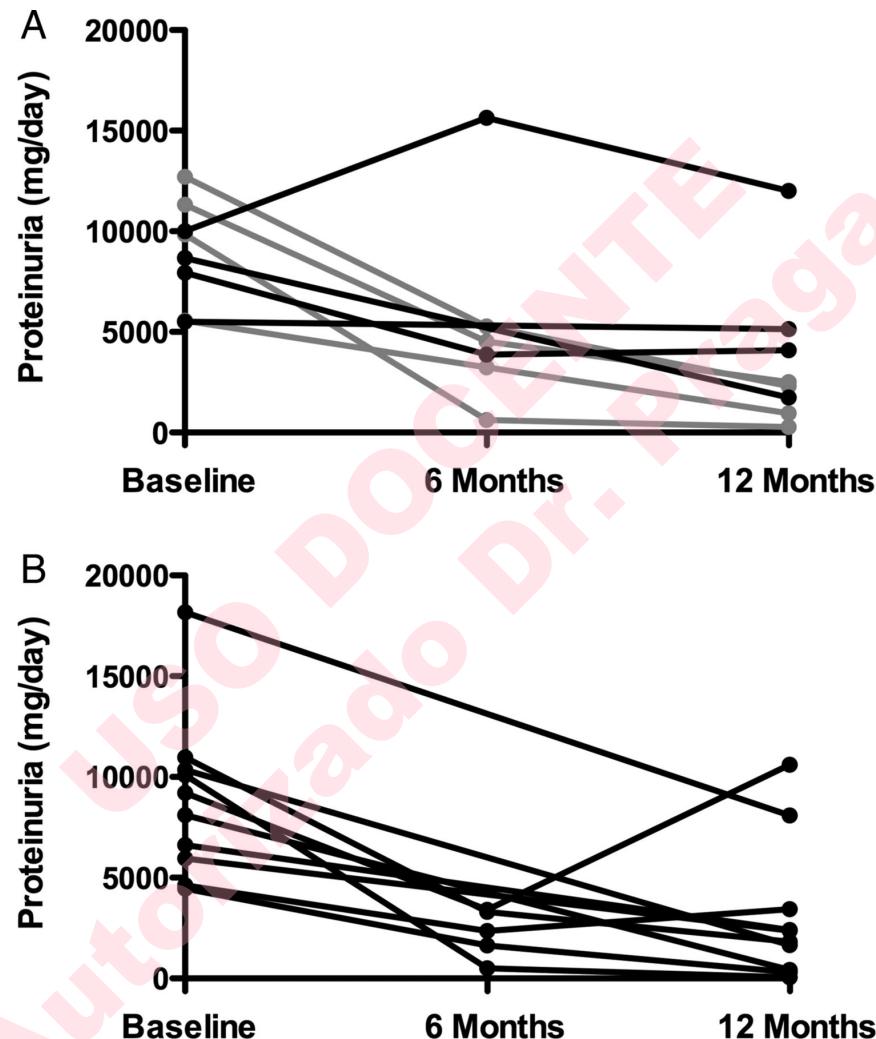


Proteinuria and cumulative ACTH dose.



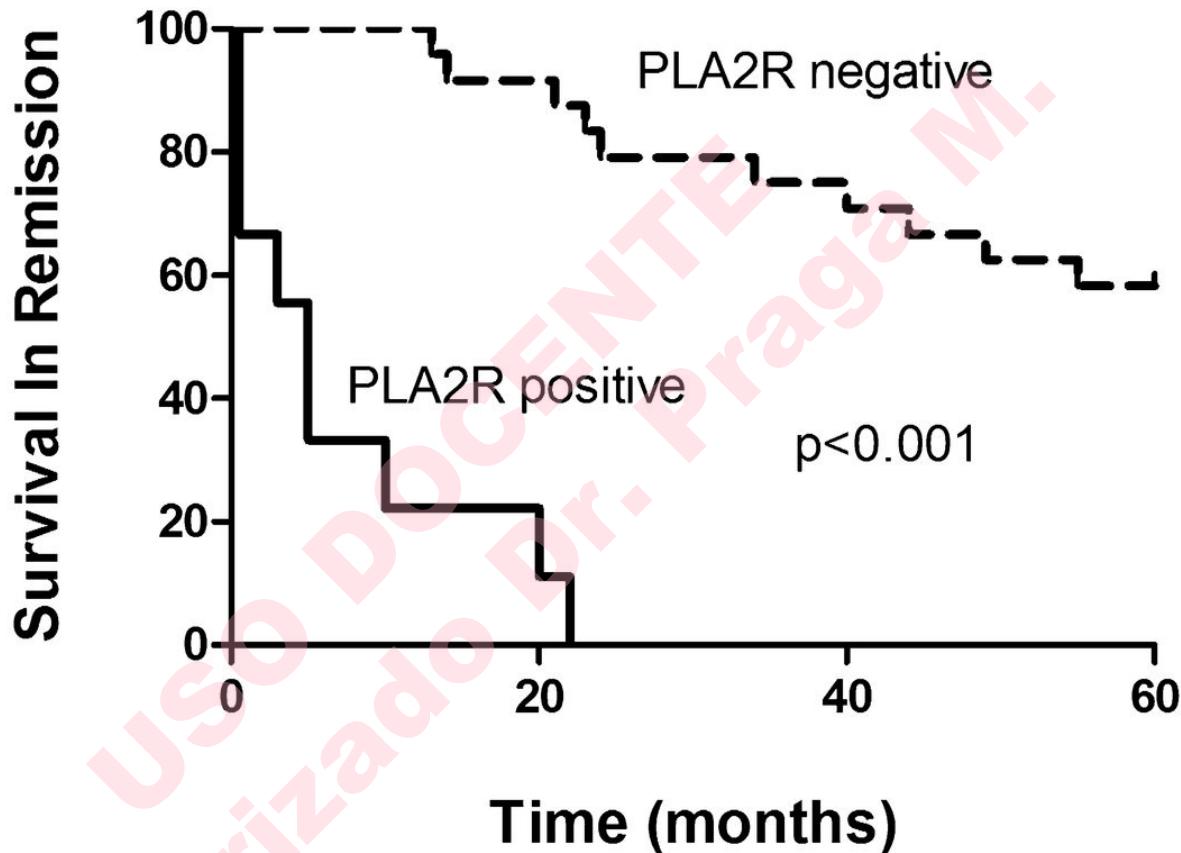
Michelle A. Hladunewich et al. Nephrol. Dial. Transplant.
2014;29:1570-1577

Proteinuria response to treatment.



Michelle A. Hladunewich et al. Nephrol. Dial. Transplant.
2014;29:1570-1577

Kaplan–Meier plot for survival in remission, grouped by PLA2R antibody status at end of therapy.



PLA2R positive
PLA2R negative

9
24

2
22

0
18

0
14

Anneke P. Bech et al. CJASN 2014;9:1386-1392