Sequential Therapy: Does it Have a Place in Membranous Glomerulonephritis Management?

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ASN 2010

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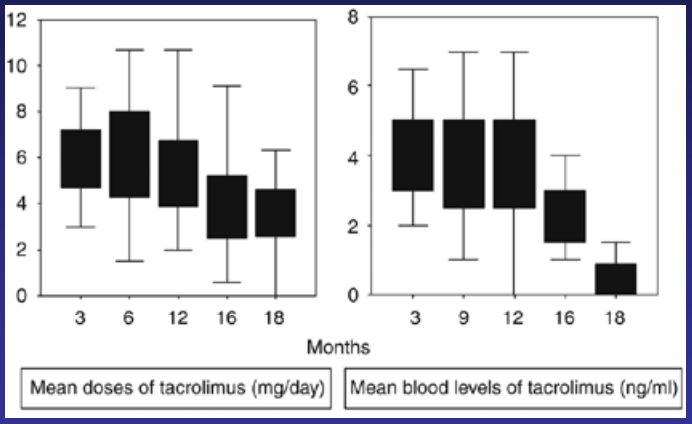
Calcineurin inhibitors (CNI) (Cyclosporin, Tacrolimus): Very effective drugs to induce remission in idiopathic membranous nephropathy (IMN)

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%

Remission can be achieved with doses and blood levels of anticalcineurinics lower than used in renal transplantation



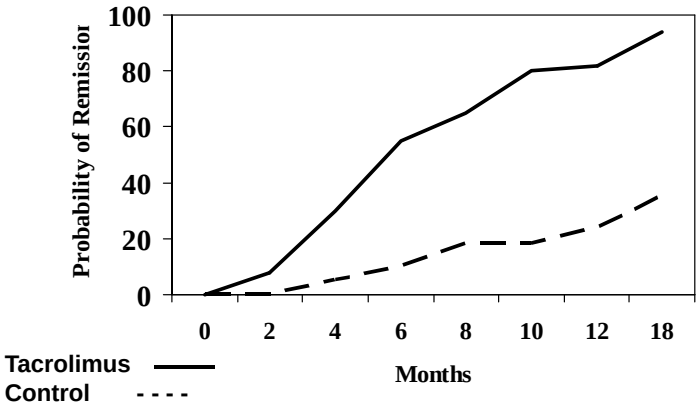
Tacrolimus monotherapy in Membranous nephropathy, Praga M, et al. Kidney Int 2007

Tacrolimus in IMN
Hospitals Vall d'Hebrón-12 de Octubre

- 65 treated patients
- Partial remission 30 (46%)
- Complete remission 23 (35%)
- No Response 12 (18%)

	Responders (PR+CR) (N=53)	Non Responders (N=12)	P
Initial Proteinuria (g/d)	8.7 ±2.9	12.8 ±5.3	<0.05
Age (yr)	46.5 ±14.1	46.7 ± 15.6	NS
Duration of Tacrolimus (mo)	17.6 ±3.3	15.8 ±3.6	NS
Blood levels (ng/ml)	5.9 ±2.1	6.8 ± 2.4	NS
Initial Scr (mg/dl)	0.99 ±0.2	1 ± 0.35	NS

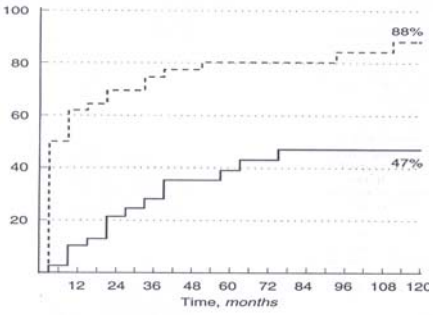
Can calcineurin inhibitors induce a more rapid remission of nephrotic syndrome in IMN than protocols based on steroids+cytotoxics?



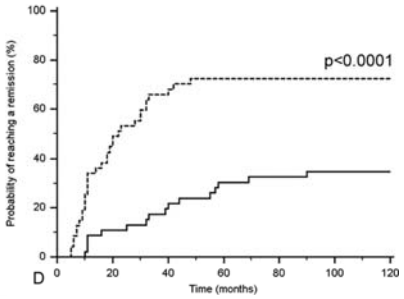
Tacrolimus
Praga et al
Kidney Int 2007

Probability of remission (either complete or partial remission) in tacrolimus-treated group (solid line) and control group (dashed line)

Can calcineurin inhibitors induce a more rapid remission of nephrotic syndrome in IMN than protocols based on steroids+cytotoxics?



Steroids+Clorambucil
Ponticelli et al Kidney Int 1995



Steroids+Cyclophosphamide
Jha et al, JASN 2007

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

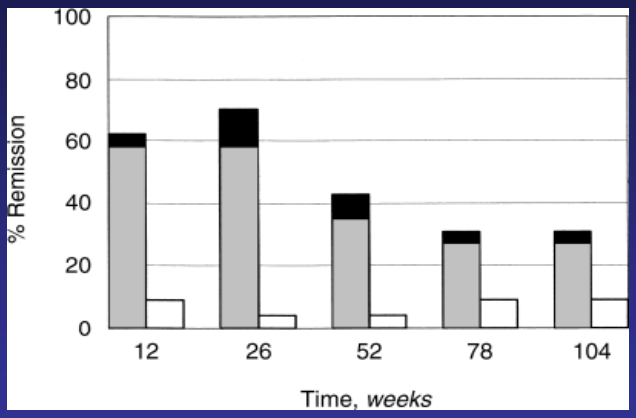
Study		CR	PR	Remission (Total)	Relapse
Cattran Kidney Int 2001	Cyclosporin	7%	68%	75%	48%
	Control	4%	17%	19%	
Praga Kidney Int 2007	Tacrolimus	32%	44%	76%	47%
	Control	13%	13%	26%	

Tacrolimus in IMN
Hospitals Vall d'Hebrón-12 de Octubre

Relapses: 24/53 (45%)

	Relapsers (N= 24)	Non Relapsers (N=29)	P
Interval onset Tacrolimus-Remission (mo)	**8.9 ± 4.5**	**5.1 ± 3**	**<0,05**
Age (yr)	47.6 ± 13.1	45.3 ± 14.8	NS
Inicial doses (mg/Kg/d)	0.048 ± 0.004	0.046 ± 0.01	NS
Initial SCr (mg/dl)	1.02 ± 0.26	0.92 ± 0.14	NS
Initial Proteinuria (g/d)	9.5 ±2.8	8.7 ±3.2	NS
Duration of Tacrolimus (mo)	19.2 ± 2.5	17.1 ± 1.9	NS
Duration of tacrolimus withdrawal (mo)	6 ± 1	6 ± 1	NS
Proteinuria at tacrolimus withdrawal (g/d)	2 ± 1.7	1.6 ± 0.7	NS

Relapse of nephrotic syndrome after CNI discontinuation in other glomerular diseases



Cattran et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. *Kidney International 56 (6), 2220-2226, 1999.*

Pathogenesis of IMN
Mechanisms of CNI antiproteinuric effect

- **Autoantibodies against M-type phospholipase A2 receptor (PLA_2R)**

  Beck, NEJM 2009

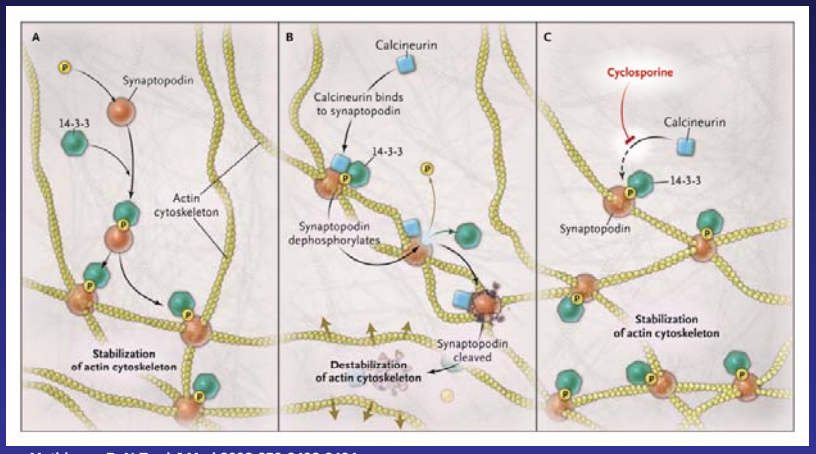
- **Immunosuppressive treatments induced a decline or disappearance of anti-PLA_2R antibodies**

  Beck, NEJM 2009

- **<u>Calcineurin inhibitors (CsA or TAC):</u>**
  - **-Decline in the production of autoantibodies ?**
  - **-Non-immunologic antiproteinuric effects?**

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

Cyclosporin in Alport Syndrome

- Cyclosporine A treatment in patients with Alport syndrome: a single-center experience.
  Massella L, Pediatr Nephrol 2010
- Resolution of proteinuria in a patient with X-linked Alport syndrome treated with cyclosporine.
  Sigmundsson TS, Scand J Urol Nephrol 2006
- Cyclosporin therapy in patients with Alport syndrome.
  Charbit M, Pediatr Nephrol 2007
- Non-immunologic mechanisms of calcineurin inhibitors explain its antiproteinuric effects in genetic glomerulopathies.
  Bensman A, Pediatr Nephrol 2010

Calcineurin Inhibitors (CNI) in IMN

How could relapses of nephrotic syndrome after CNI withdrawal be prevented?

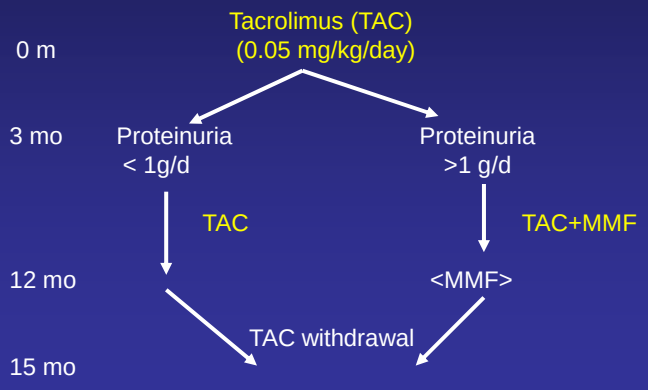
Administration of another Immunosuppressive drug during CNI tapering?

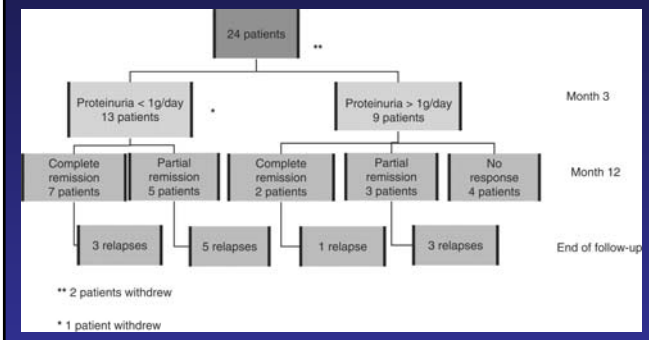
Nephrol Dial Transplant (2007) 22: 3196–3201
doi: 10.1093/ndt/gfm366
Advance Access publication 25 June 2007

Original Article

Treatment of idiopathic membranous nephropathy with the combination of steroids, tacrolimus and mycophenolate mofetil: results of a pilot study

José Ballarín, Rafael Poveda, Jordi Ara, Laureà Pérez, Francesca Calero, Josep M. Grinyó and Ramón Romero





Remission (12 m)
71%

Relapses
73%

Ballarin J et al. Nephrol. Dial. Transplant. 2007;22:3196-3201

NDT Nephrology Dialysis Transplantation

MMF to prevent relapses

- 5 patients. Partial remission of NS with tacrolimus but tacrolimus-dependence thereafter
- MMF, 1-2 g/day started at the onset of tacrolimus withdrawal (6 months) and maintained for 1 year

RESULTS

- Relapse of NS in 4/5 pts after tacrolimus discontinuation, in spite of MMF treatment.
- No relapse in 1/5

Conclusion: MMF, not effective to prevent relapses

Sequential Therapy Tacrolimus(TAC)-Rituximab (RTX) to overcome CNI – dependence in IMN

RTX in steroid-dependent nephrotic syndrome

-
- **Rituximab efficiency in children with steroid-dependent nephrotic syndrome.**
  Sellier-Leclerc A. Pediatr Nephrol 2010
- **Rituximab treatment for severe steroid- or cyclosporinedependent nephrotic syndrome: a multicentric series of 22 cases.**
  ***Guigonis V. Pediatr Nephrol 2008*.**
- **Rituximab: is replacement of cyclophosphamide and calcineurin inhibitors in steroid-dependent nephrotic syndrome possible?.**
  Dötsch J. Pediatr Nephrol 2008

Sequential therapy TAC- RTX to prevent relapses in IMN

PROTOCOL

- **13 patients with IMN and long-term dependence on treatment with CNI (tacrolimus or cyclosporin)**
- **While on partial remission with CNI treatment, RTX (375 mg/m2) weekly x 4**
- **CNI 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.

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

Sequential therapy with RTX to prevent relapses in IMN

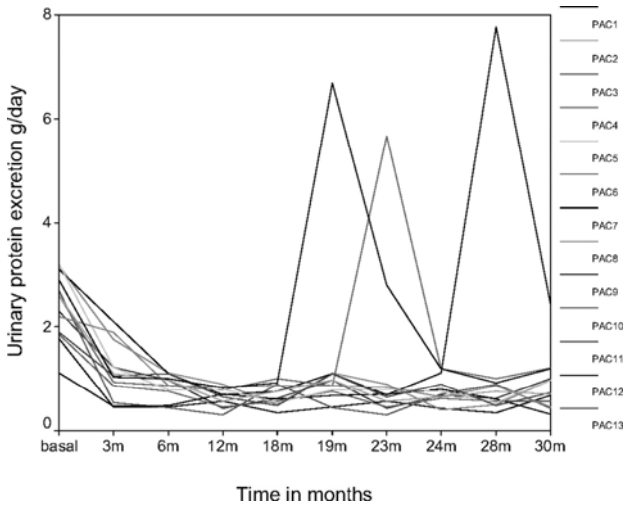
Evolution of urinary protein excretion in the whole group of patients along the 30 months period of follow-up

•p< 0,001 and ** p< 0,01 when compared to basal levels

	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*

Segarra et al, Clin JASN 2009

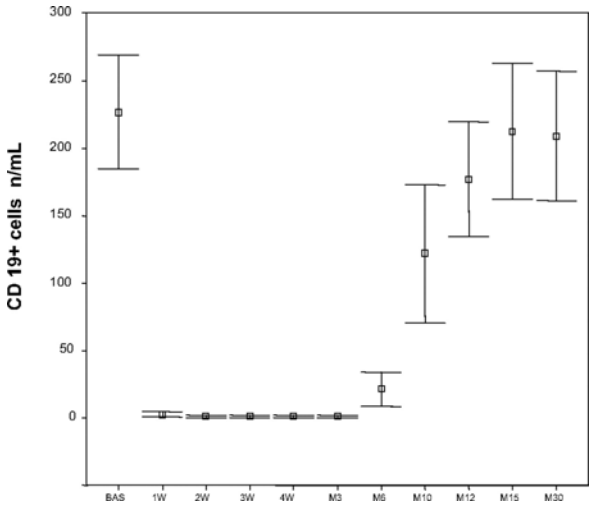
Time course of urinary protein excretion (g/24 h) in individual patients from entry into the study (basal) to end of follow-up (month 30) Values represent proteinuria in g/d



3 relapses, 19, 23 and 28 months after RTX

CJASN

Evolution of CD-19+ cell count over the total observation period



B cell recovery at 7 months (6-11 m)

CJASN

Sequential therapy TAC-RTX in IMN Hospitals Vall d'Hebrón-12 de Octubre

- **27 patients treated.**
- **All of them had responded to TAC treatment, but proteinuria relapsed after TAC withdrawal**
- **Protocol:**
  - **-Reinduction of remission with TAC**
  - **-RTX: 375 mg/m2 weekly x 4 or 1000 mgx2**
  - **-TAC tapering for 3-6 months after RTX**

Sequential therapy TAC-RTX in IMN Hospitals Vall d'Hebrón-12 de Octubre

RESULTS

- **Persistence of Remission after TAC withdrawal in all the patients, without maintenance immunosuppressive therapy.**
- **Minor side effects**

Sequential therapy TAC-RTX in IMN Hospitals Vall d'Hebrón-12 de Octubre

RESULTS

- Relapse of proteinuria in 7/27 (25%) 4,11,19,23,24,28 and 29 months after RTX. Successfully treated with a new course of TAC/RTX
- At the last follow-up:
  - -27/27 (100%) in partial remission,
  - -24 without any immunosuppression
  - -3 with low tacrolimus doses.

Rituximab in IMN

Systematic Review

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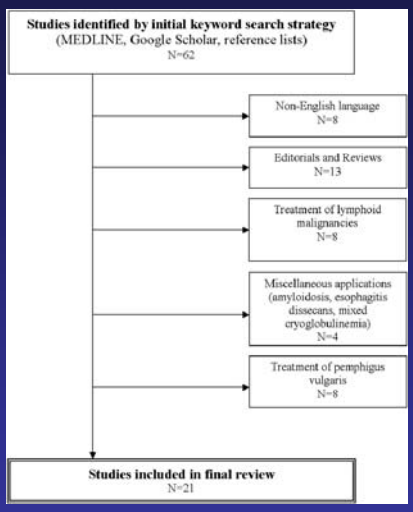
RTX
(375 mg/m2 for 4 wk
or 1 g on days 1 and 15):

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

CJASN

Why rituximab administered after tacrolimus is more effective than rituximab alone?

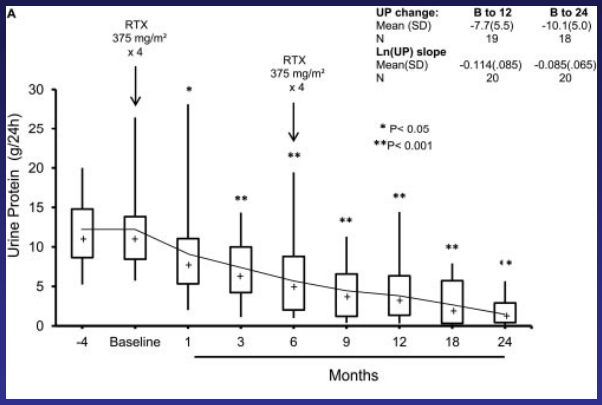
1) The antiproteinuric effect of TAC would decrease RTX losses by urine, improving its pharmacokinetic and efficacy

Why rituximab administered after tacrolimus is more effective than rituximab alone?

Fervenza F et al CJASN 2010

2 cycles of RTX (375 mg/m2x4) at 0 and 6 months

18/20 in remission at 24 mo.



Serum RTX levels, significantly lower in IMN patients than in Rheumatoid arthritis, although they increased after the 2nd cycle of RTX. These data suggest that proteinuria influences the effectiveness of RTX

Why rituximab administered after tacrolimus is more effective than rituximab alone?

2) Synergyc effect of the combination TAC-RTX, by unknown mechanisms

Rituximab in patients with limited (>50 % proteinuria decrease) or poor response to tacrolimus

Age (yr)	Crs (mg/dl)	GFR (ml/m)	Pro 0 m	Pro 6 m	Pro 12 m	Last control	Follow-up (mo)	Relapse
26	0,8	110	7,6	1,7	1,5	1,12	56	NO
31	1,1	116	9	0,6	0,5	0,81	58	Yes
29	0,98	123	6,6	0,5	0,3	0,34	53	Yes
75	1,6	62	7,8	2,9	1,6	0,9	57	NO
74	1,1	78	9,2	2,56	1,67	0,5	48	NO
73	1,3	65	6,5	0,76	0,72	0,83	49	Yes
33	1,4	119	6,3	1,9	1,3	0,56	25	NO
31	0,89	114	12,4	1,23	1,2	1,13	39	NO
43	1,25	126	4,9	0,6	0,9	0,77	48	NO

Partial remission: 9/9

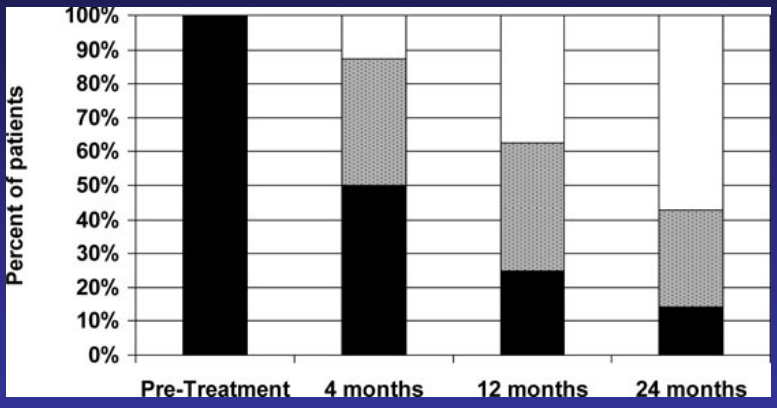
Relapses at + 17, 25, 28 months. Succesfully treated with a 2nd course of RTX

Segarra
Hospital Vall d'Hebrón

RTX in recurrent IMN after renal transplantation

- **Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation.**
  Sprangers B, Clin J Am Soc Nephrol. 2010
- **Relapse of membranous glomerulopathy after kidney transplantation: sustained remittance induced by rituximab.**
  Weclawiak H, Clin Nephrol 2008
- **Anti-CD20 monoclonal antibody (rituximab) for the treatment of recurrent idiopathic membranous nephropathy in a renal transplant patient.**
  Gallon L, Am J Transplant 2006
- **Rituximab in Recurrent Idiopathic Membranous Nephropathy.**
  El-Zoghby Z, Am J Transplant 2009

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



Changes in proteinuria following treatment with Rituximab.
Percent of patients who achieved a complete remission (CR; open bar), partial remission (PR; grey bar) or no remission (NR; black

Sequential Therapy: Does it Have a Place in Membranous Nephropathy Management? Our Current Policy (I)

Conservative Management,
(including ACEI/ARB),
Close Monitoring
Possibility of Spontaneous Remission
(30%)

Aggressive presentation:
Deteriorating renal function
massive nephrotic syndrome:
Steroids+cytotoxic
(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%)

Sequential Therapy: Does it Have a Place in Membranous Nephropathy Management? Our Current Policy (II)

TACROLIMUS

Partial, Complete or Limited
remission of NS
in a majority of
patients

→

Proteinuria relapse
during TAC tapering:
Increase of TAC doses,
RTX (375 mg/m2 x 4)
and TAC tapering
for 3-6 mo
(Sequential Therapy)

Sequential therapy TAC-RTX in IMN
Hospitals Vall d'Hebrón-12 de Octubre

Summary (I)

- Tacrolimus: High rates of rapid NS remission (complete, partial or limited) with relatively low doses and minor side effects
- Main limitation of tacrolimus: High rates of relapse after drug withdrawal

Sequential therapy TAC-RTX in IMN
Hospitals Vall d'Hebrón-12 de Octubre

Summary (II)

- Rituximab, administered when the patient is on TAC-induced partial or limited remission, effective to allow TAC discontinuation and to prevent relapses
- Sequential therapy tacrolimus-rituximab: Sustained remission in the majority of patients, without any immunosuppressive maintenance treatment and with low rates of side effects.