PREDICTORS OF RESPONSE AND RELAPSE IN PATIENTS WITH IDIOPATHIC MEMBRANOUS NEPHROPATHY TREATED WITH TACROLIMUS.

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BACKGROUND

Tacrolimus (TAC) monotherapy has been shown to be effective in the treatment of idiopathic membranous nephropathy (IMN) (Praga et al, KI 2007; 71: 924), but observational studies involving a larger number of patients have not been published.

METHODS

We performed a retrospective analysis of all IMN patients treated with TAC in 12 Spanish Hospitals.

Primary outcomes were complete (CR) or partial (PR) remission.

Secondary outcomes were relapses after TAC withdrawal and safety and tolerance to treatment.

Study baseline was defined as the onset of TAC treatment. Follow-up was 30 (14-66) months.

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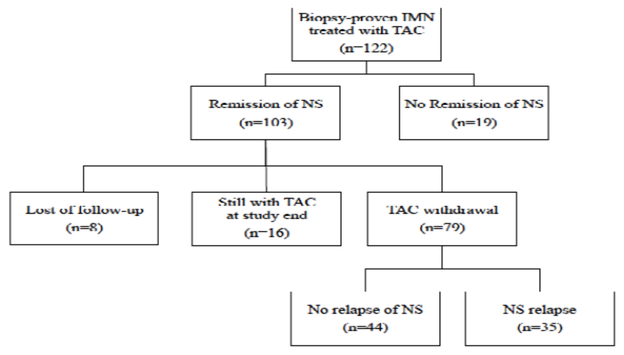


RESULTS

PATIENTS

The study collected 122 patients. Median interval between renal biopsy and TAC treatment was 9 months (6-30). 43 patients (35%) had received other immunosuppressive treatments. 94% were receiving ACEI/ARB at the onset of TAC. Renal function was stable in all of them, no patient showing renal function decline in the 6-month period before tacrolimus onset.

Initial TAC doses were 0.049 0.01 mg/kg/day, and only 10 patients were treated simultaneously with corticosteroids (CS). Mean duration of TAC treatment was 17 7 months, including a full-dose TAC period (12 5 months) and a tapering period (5 4 months).

REMISSIONS

Remission (either CR or PR) was achieved in 103 patients (84%). Time to PR was 6 (1-18) months. Time to CR was 9 (1-96) months.

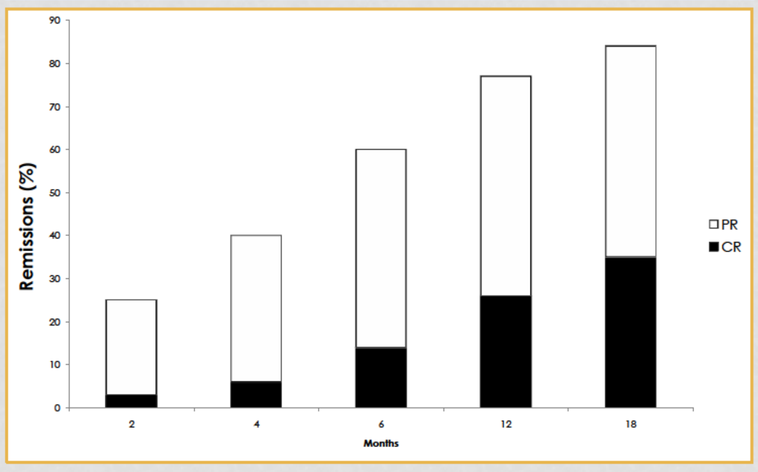
Among responders, 60 patients (58%) achieved PR and 43 (42%) CR.

By multivariable analysis proteinuria at baseline was the only factor predicting remission. The probability of remission was significantly lower in patients in the third and fourth (highest) quartiles of proteinuria, as compared to patients in the lowest quartile. Factors significantly associated to a CR were: female gender (HR 2.12; 95%CI 1.12-4.02; p 0.022) and proteinuria at baseline (HR 0.78; 95%CI 0.69-0.88; p <0.0001).

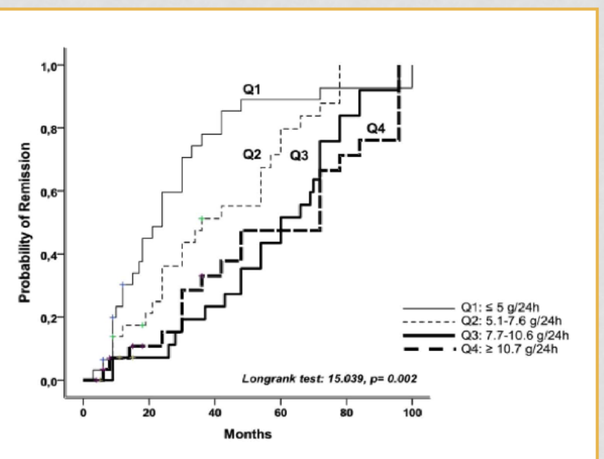
Characteristics of cohort of patients, patients who achieved remission of Nephrotic Syndrome after Tacrolimus treatment and patients without remission

Variable	Total (n=122)	Remission (n=103)	No Remission (n=19)	p-value
Mean age (years)	48 ± 13	48 ± 13	47 ± 14	n.s.
Gender male/female, n (%)	87/35 (71.3/28.7)	71/32 (68.9/31.1)	16/3 (84.2/15.8)	n.s.
Histological classification n (%)				n.s.
Stage I	37 (30.0)	29 (78.0)	8 (22.0)	
Stage II	62 (51.0)	52 (84.0)	10 (16.0)	
Stage III	22(18.0)	21 (95.0)	1 (5.0)	
Stage IV	1 (1.0)	1 (100.0)	0 (0.0)	
Mean serum creatinine (mg/dL)	1.02 ± 0.34	0.99 ± 0.29	1.18 ± 0.51	n.s.
Mean eGFR (ml/min/1.73m^2)	84.1 ± 29.8	84.5 ± 28.9	81.7 ± 35.1	n.s.
Patients with eGFR <60 (ml/min/1.73m^2), n (%)	23 (19.0)	19 (18.0)	4 (21.0)	n.s.
Proteinuria (g/d) median (IQR)	7.65 (5-10.64)	7.45 (4.91-10.23)	9.4 (6.2-12.0)	n.s.
Mean serum albumin (g/dL)	2.55 ± 0.65	2.52 ± 0.64	2.74 ± 0.74	n.s.
Time since diagnosis (renal biopsy, in months), median (IQR)	9 (6-30)	9 (6-29)	10 (6-34)	n.s.
Previous treatment with other immunosuppressive drugs (%)	43 (35.0)	34 (37.0)	9 (60.0)	n.s.
Treatment with ACEI/ARB (%)	115 (94.0)	98 (96.0)	17 (89.0)	n.s.
Treatment with corticosteroids (%)	10 (8.0)	8 (7.0)	2 (10.0)	n.s.
Mean tacrolimus initial doses (mg/d)	0.049 ± 0.01	0.05 ± 0.01	0.042 ± 0.02	n.s.
Mean tacrolimus doses during treatment (mg/kg/d)	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	n.s.
Mean tacrolimus blood levels (ng/dL)	6.85 ± 1.89	6.78 ± 2.17	6.86 ± 1.76	n.s.
Tacrolimus nephrotoxicity n (%)	8 (7.0)	5 (5.0)	3 (16.0)	n.s

Percentage of Complete (black) and Partial (white) remissions after the onset of Tacrolimus treatment



Probabilities of remissions according to the level of proteinuria



RELAPSES

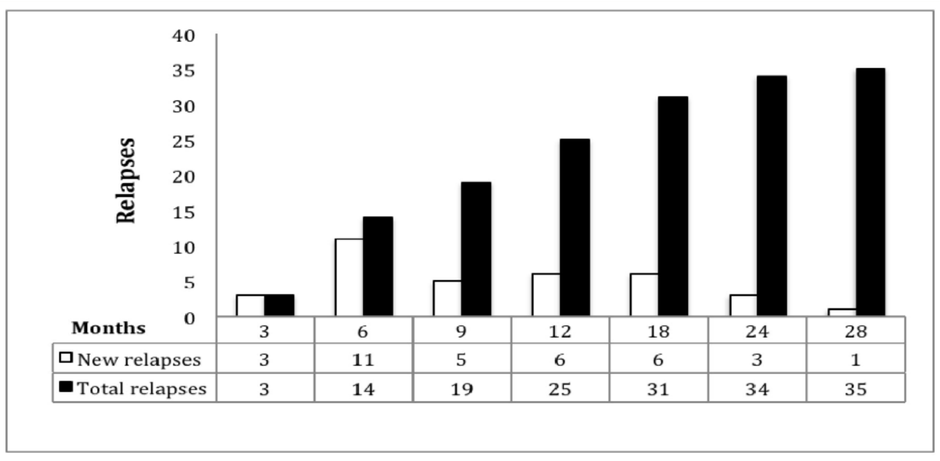
After 30 (14-66 month), months of follow-up, 44% of patients who had achieved CR/PR, relapsed.

Median time to relapse after the onset of TAC tapering was 9.5 months (3-18). Most of relapses ocurred during TAC tapering or shortly after its discontinuation.

Relapses appeared earlier in PR than in CR: 8.5 (3-26) vs 20 (6-62) months after the onset of TA tapering, p= 0.024.

By multivariable analysis PR at the onset of TAC tapering and shorter duration of TAC tapering were factors significantly associated with relapses.

Monthly and cumulative number of relapses after the onset of Tacrolimus tappering



Months	3	6	9	12	18	24	28
New relapses	3	11	5	6	6	3	1
Total relapses	3	14	19	25	31	34	35

ADVERSE EVENTS

Adverse Event	n (%)
Nephrotoxicity	
- Patients with≥ 50% increase of serum creatinine after the onset of tacrolimus treatment	8 (6%)
- Tacrolimus withdrawal because nephrotoxicity	4 (3%)
Infections	
- Mild (ambulatory treatment)	9 (7%)
- Moderate (hospitalary treatment)	2 (1.6%)
Neurological	
- Focal seizures	1 (0.08%)
- Headache	1 (0.08%)
- Tremor	5 (4%)
Cardiovascular	
- Myocardial infarction	1 (0.08%)
- Stroke	3 (2.4%)

FINAL OUTCOMES

	No Relapsing patients (n= 44)	Relapsing patients (n= 35)	p
End Renal Stage Disease	0	2 (6 %)	ns
Doubling of Serum creatinine	0	6 (17,1%)	0,021

CONCLUSIONS

- TAC monotherapy induces a high number of remissions (84%) in IMN with stable renal function, and was well tolerated.
- Lower proteinuria at the onset of treatment predicted nephrotic syndrome remission.
- Relapses were common (44%) and associated with the presence of PR at the onset of TAC tapering. A shorter duration of TAC tapering increased the probability of relapse.
- New strategies to avoid relapses after TAC withdrawal should be investigated.

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