



# Amyloid

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## Transthyretin (ATTR) amyloidosis nephropathy: lessons from a TTR stabilizer molecule

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### Background

Tafamidis delayed neuropathic progression in patients with transthyretin amyloidosis [1], but long-term effectiveness in multisystem commitment is unclear. In renal involvement, albuminuria represents the first stage of clinical nephropathy with progression to nephrotic proteinuria and end-stage renal disease as natural course of the disease. The distribution of amyloid deposits is according to the grade of proteinuria; glomerular and vascular involvement predominates in proteinuric patients [2]. No effective treatment exists for renal disease. The survival on dialysis is poor, and liver and kidney transplantations are reserved for a strict number of patients. Clinical trials of approved anti-amyloid drugs were never applied to patients with severe nephropathy then, effectiveness in kidney disease is unclear. This study investigates the long-term effects of tafamidis on patients who had kidney transthyretin amyloidosis in terms of kidney function and proteinuria.

### Materials and methods

An open-label, nonrandomized, prospective evaluation was conducted. Twelve patients (11 female, 1 male), with neuropathy stage I and estimated glomerular filtration rate (eGFR)  $\geq 60$  mL/min, were treated with tafamidis, receiving 20 mg QD. Kidney function was evaluated by measuring creatinine and cystatin C. Proteinuria and urine creatinine were measured in a spot urine collection. Determinations and patient clinical evaluation were made at baseline and at all subsequent visits every 6 months. We also divided the patients into two groups on the basis of final proteinuria: 5 patients with proteinuria  $<30$  mg and 4 patients with proteinuria  $>30$  mg, and compared them. The unpaired Student's *t*-test

and the nonparametric Wilcoxon–Mann–Whitney test were used to determine the significance of differences.

### Results

Nine patients completed 36 months of therapy, 2 patients completed 30 months and 1 patient completed 18 months. The mean age was  $51 \pm 11$  years at the time tafamidis was begun and the mean duration of neuropathy was  $5 \pm 4$  years. Two patients had kidney biopsies, all had transthyretin amyloidosis. Only one patient was under an angiotensin-II inhibitor. During the study period, kidney function remained stable with sustained reductions in proteinuria (Table 1). GFR calculated using CKD-EPI, MDRD and Cockcroft-Gault formulas was, respectively, at enrollment and at the end of follow-up of 98.8 and 98.4, 95.8 and 95.3, 83.1 and 80.5 mL/min. The patients with proteinuria  $>30$  mg had higher significant values of creatinine and cystatin C across all assessments (Table 2).

### Discussion and conclusions

Over the course of 36 months of tafamidis, there was no change in kidney function with sustained reduction in proteinuria. This suggests that tafamidis may slow or halt kidney disease demonstrating the feasibility of this therapy in patients with kidney transthyretin amyloidosis. It should be used before extensive kidney damage occurs as anticipated by the higher reduction of proteinuria in patients with lower levels of creatinine and cystatin C. This is a new facet of the

Table 1. Proteinuria and urine protein/creatinine ratio.

	Mean	Standard deviation	<i>t</i>	<i>p</i> Values	<i>W</i>	<i>p</i> Values
Proteinuria (mg)			5.3	0.0004	54	0.002
Baseline	1099.1	607.9				
Month 36	64.5	94.9				
Urine protein/creatinine ratio			3.9	0.002	45	0.002
Baseline	0.93	0.56				
Month 36	0.22	0.14				

Table 2. Comparison between patients with proteinuria <30 mg (group I) and > 30 mg (group II).

	Creatinine (mg/dl)					Cystatin C (mg/L)				
	Mean ± SD	t	p Values	W	p Values	Mean ± SD	t	p Values	W	p Values
Baseline										
I	0.60 ± 0.13	−2.1	0.08	4	0.18	0.66 ± 0.12	−2.9	0.04	0	0.06
II	0.77 ± 0.11					0.93 ± 0.12				
Month 6										
I	0.55 ± 0.16	−2.5	0.05	2	0.06	0.66 ± 0.08	−3.4	0.04	0	0.06
II	0.75 ± 0.07					0.98 ± 0.15				
Month 12										
I	0.59 ± 0.14	−2.7	0.04	0	0.02	0.67 ± 0.09	−5.1	0.002	0	0.03
II	0.88 ± 0.17					1.00 ± 0.09				
Month 18										
I	0.57 ± 0.12	−3.3	0.02	1	0.03	0.64 ± 0.06	−5.5	0.004	0	0.03
II	0.85 ± 0.13					1.01 ± 0.12				
Month 24										
I	0.61 ± 0.17	−2.6	0.04	2	0.06	0.69 ± 0.14	−3.2	0.02	0	0.02
II	0.85 ± 0.11					0.99 ± 0.14				
Month 30										
I	0.55 ± 0.13	−2.6	0.04	1	0.03	0.74 ± 0.11	−4.4	0.004	0	0.02
II	0.83 ± 0.18					0.98 ± 0.06				
Month 36										
I	0.60 ± 0.12	−2.7	0.03	0	0.02	0.70 ± 0.12	−2.6	0.04	2	0.06
II	0.89 ± 0.10					0.93 ± 0.15				

drug, since previous clinical trials did not include nephropathy as an end-point of treatment.

Declaration of interest

Dr Coelho has served on the speakers bureau of Pfizer Inc. The other authors report no conflicts of interest.

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