Effects of Transthyretin Stabilizer - Tafamidis on ATTR Amyloidosis Renal Damage: persistent reduction of albuminuria

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Introduction

The TTR amyloidoses (ATTR) are rare diseases that cause the most common type of autosomal-dominant systemic amyloidosis. ATTR is reported as a worldwide rare disease, especially manifested as polyneuropathy and cardiomyopathy. TTR is a major protein mainly synthesized by the liver and forms a homotetramer that acts as a plasma transport protein. Destabilization of TTR tetramers into monomers is a critical step in TTR amyloid formation. Tafamidis, a small-molecule ligand that occupies the thyroxine-binding sites with negative cooperativity, kinetically stabilizes the tetramer and inhibits the protein dissociation into monomers. It was the first drug approved in Europe in stage 1 neuropathy (walking unaided) to slow progression of the disease (1). Liver transplantation was assumed as the standard therapy in the last 25 years.

The renal disease encompasses varying degrees of albuminuria and progression to stage 5 renal disease. The distribution of amyloid deposits is according to the grade of proteinuria; glomerular and vascular involvement predominates in proteinuric patients.

Although neuropathy in ATTR V30M amyloidosis begins at thirties, the presentation of neurologic disease in nephropathic patients appears especially in older ones, without a clear family history, atypical clinical picture and in female gender (2). No effective treatment exists for renal disease. The survival on dialysis is poor and liver-kidney transplantation is reserved for a strict number of patients. Clinical trials of approved anti-amyloid drugs were never been applied to nephropatic patients then, effectiveness in kidney disease is unclear.

Objective

This study investigates the long-term effect of tafamidis in albuminuria and in glomerular filtration rate (eGFR) in a cohort of neuropathic patients with hereditary ATTR V30M amyloidosis in an early stage of neuropathy.

Methods

A prospective, single centre, non-randomized cohort study was conducted. Men and nonpregnant women aged 18-75 years were eligible if they had neuropathy stage I, biopsy-confirmed ATTR amyloidosis, urinary albumin-to-creatinine ratio (UACR) > 300 mg/g and eGFR ≥ 60 mL/min. Exclusion criteria were *TTR* variants other than V30M, renal or liver transplant, hepatitis B, C, HIV and diabetes mellitus. Patients who had participated in any other study of an investigational drug were also excluded.

The study was initiated in July 2012 and all patients that started tafamidis therapy were evaluated until July 2014. All patients received tafamidis 20 mg QD. Clinic visits and laboratory evaluations were scheduled at baseline, months 6, 12, 18 and 24. The changes from the pretreatment baseline to the end of the study by each period were compared using the Wilcoxon rank sum test.

Results

Ninety eight patients (54 males, 44 females) were screened; 22 meet the inclusion criteria. Amyloid was demonstrate: 17 patients in salivary glands, 3 in salivary glands and kidney, 1 in sural nerve and 1 in the skin.

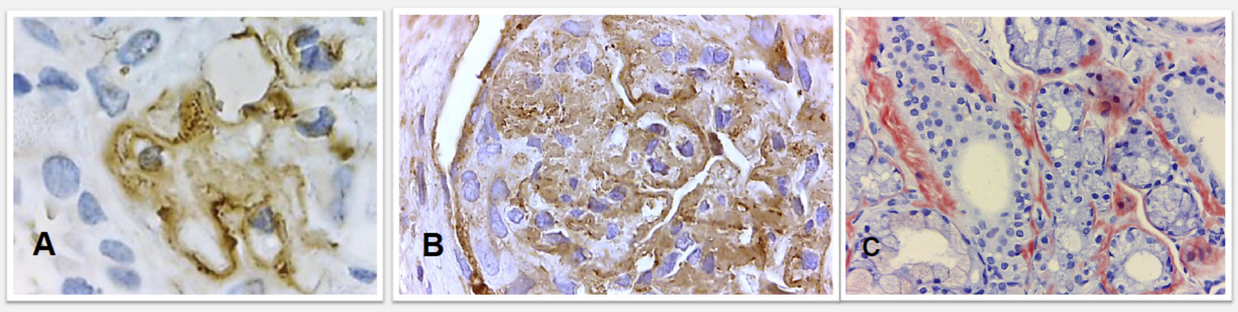

Figure 1: Light microscopy: A) and B) Glomerular basement membrane and mesangial areas; ATTR amyloidosis, anti-TTR fixation, immunoperoxidase technique, original magnification x1000. C) Amyloid deposits in salivary gland Congo red stained positive material x400.

Table I: Patient demographic characteristics at baseline.

Number of patients (n)	22
Age (years, mean ± SD)	51.4±12.1
Female: n (%)	18 (81,8)
Evolution of neuropathy (years, mean ± SD)	4.5±3.7
Age of onset of neuropathy (years, mean ± SD)	47±12.3
Angiotensin-II inhibitor/angiotensin II-AT1 receptor blockers (n)	3

Table I: Evaluation of 10 patients that completed 24 months of follow-up.

Median (IQR)	Baseline	Month 12	*P*
Creatinine (mg/dl)	0,69 (0,45-0,90)	0,74 (0,39-0,99)	0,38
Cockcroft-Gault (ml/min/1,73 m²)	83,6 (53,8-143,2)	81,8 (46-137,1)	0,13
MDRD (ml/min/1,73 m²)	93,0 (66,8-160,5)	82,9 (58,9-174,2)	0,19
EPI (ml/min/1,73 m²)	105,1 (75,9-132,1)	95,2 (65,7-128,4)	0,13
Serum albumin (g/dl)	3,60 (2,82-4,10)	4,11 (3,63-4,63)	< 0,01

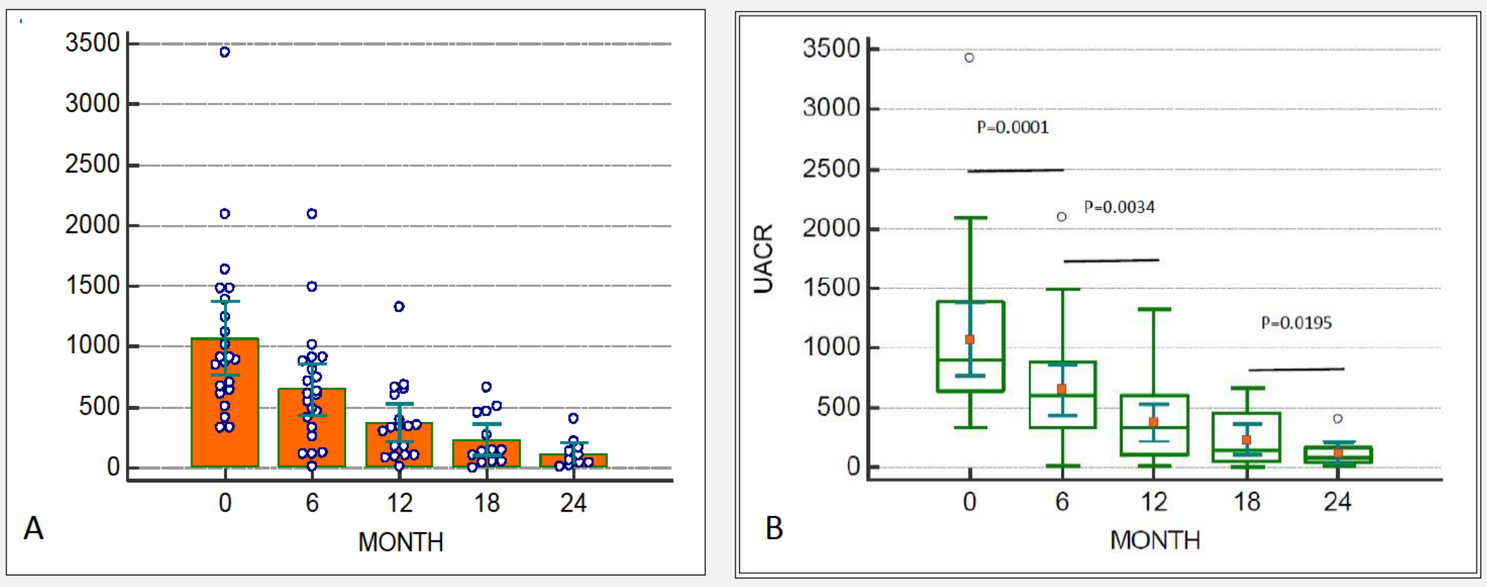

Figure 2: A) and B) Decreasing levels of urinary albumin-to-creatinine ratio (UACR) after tafamidis in treatment-naive patients with hereditary ATTR V30M amyloidosis; 0 represents the baseline.

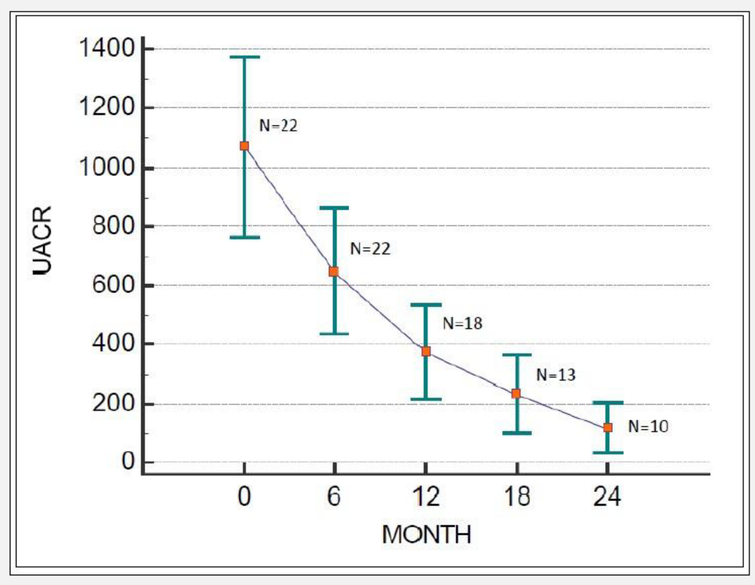

Figure 3: Number of patients evaluated in the course of the follow-up; 0 represents the baseline.

Conclusions

- In hereditary ATTR V30M amyloidosis, tafamidis 20 mg QD decreases albuminuria with stable renal function.
- The treatment effect was sustained over 24 months and proved to be save, without additional renal disease.
- This is a new facet of the drug, since previous clinical trials did not include nephropathy as an end-point of treatment.
- Our findings suggest that recovering the quaternary structure stability of ATTR is critical to retard kidney amyloidosis.
- In a near future, we should compare if benefit (or not) in different organs an systems evolves in a homogeneous mode.

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References

1) Coelho T, Maia LF, da Silva AM, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. J Neurol. 2013, 260(11):2802-14

2) Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. Clin J Am Soc Nephrol. 2012; 7(8): 1337-1346

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