Tafamidis for a Transplant Patient with Transthyretin Amyloid Polyneuropathy

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Dear Editor,

Transthyretin (TTR) familial amyloid polyneuropathy (FAP) is an autonomic and peripheral sensorimotor autosomal dominant hereditary neuropathy that produces progressive disability and shortened life expectancy. Tetramer dissociation of TTR in monomers is the limiting step in the pathogenesis of TTR-FAP.¹ Liver transplantation (LT) has been considered the optimal etiological treatment.² However, the release of TTR by the choroid plexus³ and the continuous deposition of wild-type TTR produce cerebral amyloid angiopathy (CAA)⁴ and the progression of neuropathy⁵ in some individuals after LT. Tafamidis is a specific stabilizer of the TTR tetramer that has recently been shown to be effective in preventing progression in nontransplant patients affected by TTR-FAP.⁶ There are no previous reports of its use in patients after LT progression.

A 57-year-old Spanish female was examined for autonomic dysfunction in 2004 because of urinary and fecal incontinence at night and orthostatic hypotension with reversed blood flow in the end-diastolic phase when tilted to a position 70° from upright. She underwent pacemaker implantation for atrioventricular block. The patient was a Val30Met carrier with TTR-FAP. Her family history included a deceased, previously ill mother from Majorca and a sister who underwent combined liver-and-kidney transplantation, both affected by the same disease. She was still asymptomatic in 2006, and the findings of EMG and a nerve conduction study (NCS) were normal. LT was performed in 2006.

In 2012, the patient began to note symptoms of distal hypesthesia in both feet. A neurological examination showed the bilateral absence of Achilles reflexes, and an NCS revealed reduced sensory responses in the lower limbs. Her condition deteriorated 2 years later, with spreading of the hypesthesia to the hands, slight weakness in the lower limbs, and exercise-induced dizziness that did not hinder her ability to walk. A follow-up NCS revealed progression with generalized sensorimotor polyneuropathy in the lower and upper limbs, with primary involvement at the distal level. During 2013 and 2014 the patient suffered from several transient focal neurological episodes (TFNE) of unilateral headache, aphasia, and right hemiparesis that lasted from 5 to 30 minutes with a frequency of once every two weeks. She had no vascular risk factors or previous history of migraine. The findings of brain MRI with angiography and EEG were normal, and so these episodes were interpreted as symptoms of incipient CAA. The patient also suffered from glaucoma related to TTR deposition, and a trabeculectomy was performed in 2013.

Since the reported clinical and neurophysiological deterioration had started 5 years after transplantation, when the clinical stage of the patient on the Coutinho scale for TTR-FAP had changed from 0 to 1, oral tafamidis was administered at 20 mg once daily from January 2015. The patient was followed up regularly for 18 months as the duration of the pivotal assay of tafamidis. Efficacy measures included changes in the Neuropathy Impairment Score-Lower Limbs (NIS-LL) and Karnofsky Performance Scale Index of functional impairment,

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Fig. 1. The figure shows scores on (A) NIS-LL, (B) NQOL, (C) Karnofsky Performance Scale Index of functional impairment, (D) R-ODS score scales and (E) mBMI. mBMI: Body Mass Index modified by total protein, NIS-LL: Neuropathy Impairment Score-Lower Limbs, NQOL: Norfolk Quality of Life-Diabetic Neuropathy Questionnaire, R-ODS: Rasch-built Overall Disability Scale.

and in the scores for the Norfolk Quality of Life-Diabetic Neuropathy Questionnaire (NQOL) and the Rasch-built Overall Disability Scale (R-ODS) between prior to initiating treatment and every 6 months from baseline up to a 18-month follow-up. The NIS-LL and NQOL score worsened from baseline to month 18 by less than 2 points, and there were no changes in the Karnofsky or R-ODS score. The nutritional status as assessed using the body mass index modified by total protein showed a slight improvement (Fig. 1). There was no further clinical deterioration. Tafamidis was well tolerated, without side effects or adverse events such as TFNE. The findings of blood counts and biochemistry analyses, including for liver and kidney function, were normal.

This study has provided the first data on the use of tafamidis in a TTR-FAP patient previously treated with LT. Tafamidis was administered after the neurological status had deteriorated, and was found to be safe with the patient considered a treatment responder for the first 18 months. Further studies should evaluate the clinical use of combined treatment in Val30Met and other mutations. CAA is observed in TTR-FAP patients with several specific TTR gene mutations, but develops only rarely in FAP patients with Val30Met, which is the most common mutation found worldwide.⁷ The potential role of tafamidis in preventing and stabilizing CAA in TTR-FAP patients carrying Val30Met has not been studied; however, the present case suggests that tafamidis could be beneficial in

remitting TFNE after LT in TTR-FAP patients with Val30Met. The intraventricular administration of a specific antisense oligonucleotide for TTR in the brains of transgenic mice with a mutated human TTR gene recently resulted in dose-dependent decreases in TTR expression in the choroid plexus.⁸ Further large-scale longitudinal studies are needed to elucidate whether tafamidis could affect the stabilization of TTR expression in the choroid plexus of FAP patients.

Conflicts of Interest

The authors have no financial conflicts of interest.

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