Drug, Healthcare and Patient Safety

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REVIEW

Updated Evaluation of the Safety, Efficacy and Tolerability of Tafamidis in the Treatment of Hereditary Transthyretin Amyloid Polyneuropathy

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Abstract: Hereditary amyloid transthyretin (ATTRv) amyloidosis is a devastating hereditary multisystemic disease affecting predominantly the peripheral and autonomic nervous systems and the heart. ATTRv is caused by mutations in the *transthyretin* (*TTR*) gene, leading to extracellular deposition of amyloid fibrils in multiple organs including the peripheral nervous system. If untreated, it is associated with a fatal outcome 10–12 years after disease onset. Different treatments are available for patients with ATTRv polyneuropathy. Tafamidis 20 mg is approved in Europe since 2011 for early stages of ATTRv polyneuropathy (stage I – able to walk without support) and it is recommended as first-line therapy in these patients. Tafamidis is a TTR stabilizer that selectively binds to TTR and kinetically stabilizes both wild-type native TTR and mutant TTR. Consequently, it has the potential to prevent the amyloidogenic cascade initiated by TTR tetramer dissociation into its monomers and subsequent misfolding and aggregation. Tafamidis is an oral drug, taken once per day, with proved efficacy, safety and tolerability in ATTRv-PN patients as demonstrated in different clinical trials and open-label extension studies as well in clinical practice setting with around 10 years of experience. Tafamidis treatment started in the earliest stages of the disease is associated with better neurological outcomes. A multidisciplinary approach in referral centres is also fundamental for monitoring patients to assess individual response to treatment.

Keywords: hereditary amyloid transthyretin amyloidosis, transthyretin, tafamidis, familial amyloid polyneuropathy, amyloidosis, TTR stabilizer

Introduction

Hereditary amyloid transthyretin (ATTRv) amyloidosis with polyneuropathy (ATTRv-PN), also commonly known as familial amyloid polyneuropathy (FAP), is a devastating hereditary multisystemic disease leading to progressive disability with a fatal outcome after 10–12 years of disease onset, if left untreated.[1] The disease is characterized by deposition of amyloid fibrils in different organs and tissues, being the peripheral and autonomic nervous systems and the heart the main afflicted organs.[2] It results from mutations in the *transthyretin* (*TTR*) gene, with an autosomal dominant inheritance, which will be responsible for the destabilization of the tetrameric structure of TTR protein with consequent dissociation into its monomers and further misfolding and formation of the amyloid fibril aggregates.[3]

In the last decades, different disease-modifying treatments have been proven to be effective and safe in attenuating disease progression.[4] Liver transplantation (LT) was the first approved treatment by eliminating the production of the amyloidogenic mutated TTR produced by the liver.[5] However, although its efficacy, there are some limitations: it is a major surgical procedure inevitably associated with its inherent risks; there is a limited number of compatible grafts; some patients still have disease progression due to continued amyloid fibril formation of wild-type TTR; amyloid fibril production in the eye and choroid plexus endures contributing to severe eye and central nervous system involvement in the later stages of the disease.[6] For these reasons, there was an active need for development of new treatments. Considering the pathogenic TTR pathway, stabilizing the mutant TTR protein, and then preventing its dissociation and

Received: 12 November 2022
Accepted: 26 January 2023
Published: 17 February 2023

consequent amyloid fibril formation, would be an optimal target for newer agents.[7] Oral TTR stabilizers (such as Tafamidis) were then developed and approved for the early stages of the disease.[7] Tafamidis 20 mg, available as a soft capsule taken once per day, was initially approved for commercial use in Europe in 2011 and then approved in other countries such as Japan, Mexico and Argentina, being currently available in more than 40 countries in where it is used as a first-line treatment in the early stage (stage I – able to walk without support) of the disease.[8] More recently, genetic modifiers agents were also approved for ATTRv-PN with encouraging results and safety.[9,10] In this review, we will assess the discovery and development of Tafamidis as a TTR stabilizer and the clinical data available to date regarding its efficacy, safety and tolerability showed in the clinical trials and in the real-world experience studies. Additionally, considering the recent emergence of new disease modifying drugs, the current role of Tafamidis and future perspectives, in the treatment hereditary transthyretin amyloid polyneuropathy, will be further analysed.

Tafamidis Development and Mechanism of Action

TTR (previously known as pre-albumin) is a tetrameric protein responsible for the transportation of holo-retinol binding protein.[11] Additionally, it is also a minor carrier (<1%) of thyroid hormone thyroxine (T4) in the blood. However, the majority of thyroid hormones are carried by albumin or thyroid-binding globulin, leaving most T4-binding sites on TTR unoccupied.[11] After understanding the amyloidogenic mechanism behind formation and aggregation of TTR amyloid fibrils, the dissociation of TTR into its monomers was found to be the first and slowest step in the pathogenic pathway, representing a potential target for newer drugs.[12] All these findings impelled the development of TTR kinetic-stabilizing agents – small agents able to selectively bind to native TTR tetramer, over the dissociative transition state, at the T4 binding sites, consequently slowing TTR dissociation and further preventing TTR aggregation.[13] Several TTR stabilizers have been reported, namely nonsteroidal anti-inflammatory drugs (NSAIDs) such as diflunisal. However, its associated toxicity to ATTR patients with cardiomyopathy demanded the development of safer and more tolerable drugs.[14] Tafamidis, or 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid, was then developed and proved to selectively bind TTR and stabilize both wild-type TTR and mutant TTR.[15] A previous study also showed that Tafamidis was able to stabilize the two most frequent mutations, Val30Met and Val122Ile, in the same way as wild-type TTR.[15] The rate of tetramer dissociation also decreases in a dose-dependent fashion. In Phase II clinical trials conducted in healthy volunteers, tafamidis meglumine 20 mg administered orally once a day exhibited a favourable pharmacokinetic profile with excellent tolerability and safety.[16]

Tafamidis Efficacy

Tafamidis efficacy in ATTRVal30Met-PN patients was first assessed in an 18-month double-blind and placebo-controlled trial (Fx-005 trial).[17] Longer-term data became available from the subsequent extension studies (Fx-006 and Fx-1006A).[18,19] The effect of tafamidis in slowing neuropathy progression rate was also evaluated in non-Val30Met patients in an open-label single treatment-arm trial (Fx1a-201) and further assessed in the extension study (Fx-1006A).[19,20] A different small, open-label and single-arm trial was also conducted in Japanese patients with predominantly Val30Met mutation[21] (Table 1). Tafamidis efficacy was additionally confirmed in a series of post hoc analysis of the key clinical trials and data from real-word experience clinical studies.[22–32]

Clinical Trials and Extension Studies

Fx-005 Trial

Fx-005 trial was a multicentre, randomized, double-blind, controlled trial that evaluated the efficacy and safety of 18 months of tafamidis treatment in 128 patients with early-stage Val30Met ATTRv polyneuropathy.[17]

Patients with stage 1 (able to walk without support) sensorimotor or autonomic neuropathy, aged 18–75 years, with documented Val30Met mutation, biopsy confirmed amyloid deposits and with a Karnofsky performance status ≥50 were included. Exclusion criteria included the presence of other causes of neuropathy, liver or kidney dysfunction, prior LT and heart failure with New York Heart Association (NYHA) status ≥ 3. Patients were randomized in a 1:1 ratio receiving either once-daily tafamidis 20 mg or matching placebo.[17]

Table 1 Summary of Tafamidis Clinical Trials and Open-Label Extension Studies

Clinical Trials	Study Design	Study Population	Primary Endpoints	Adverse Events	Outcomes
Fx-005[17]	Phase II/III Randomized, placebo-controlled double-blind trial Treatment: Tafamidis 20 mg once a day for 18 months	128 patients with documented V30M mutation and biopsy-confirmed amyloid deposits	NIS-LL Norfolk QOL-DN	AEs and SAEs incidence was similar in both groups Most frequent AE in tafamidis group was urinary tract infection	EE population: *NIS-LL responders*: 60% in tafamidis group versus 38.1% in placebo group (p=0.041). *Norfolk QOL-DN change from baseline*: 0.1 in tafamidis group versus 8.9 in placebo group (p=0.045).
Fx-006[18]	Single-arm open-label extension study of Fx-005 Treatment: Tafamidis 20 mg once a day for 12 months	86 patients with documented V30M mutation and biopsy-confirmed amyloid deposits	NIS-LL Norfolk QOL-DN	No additional adverse events	Sustained beneficial effect of tafamidis after 30 months of treatment. Patients who switched from placebo to treatment arm had slowing of disease progression Early treatment was associated with better outcomes.
Fx1A-201[20]	Phase II, open-label, single-arm study Treatment: Tafamidis 20 mg once a day for 12 months	19 ATTRv patients excluding V30M and V122I mutations	TTR stabilization at 6 weeks	Most common reported AEs: Falls (24%), diarrhoea (24%), extremity pain (19%)	*TTR stabilization* at Week 6 was achieved in 18 patients (94.7%).
Fx-1006A[19,22]	Phase III, open-label extension study Treatment: Tafamidis 20 mg once a day for up to 10 years	Patients from Fx-005, Fx-006 (75 patients) and Fx1A-201 (18 patients) trials	NIS-LL Norfolk QOL-DN Death	No additional adverse events No deaths were considered related to tafamidis	*Fx1A-303* – interim analysis up to 6 years: - All patients developed in some degree disease progression. - Rate of disease progression was similar in patients from P-T and T-T groups. - Less neurologic deterioration was seen in patients who were treated earlier with tafamidis. *Survival analysis* up to 8.5 years - 85% of V30M patients and 75% of non-V30M patients were alive at 9 and 8 years, respectively.
Japanese trial[21]	Single-arm, open-label multicentre study Treatment: Tafamidis 20 mg once a day for up to 3 years	10 Japanese ATTRv V30M and non-V30M patients with biopsy-confirmed amyloid deposits	TTR stabilization at 8 weeks	Most common reported AEs: nasopharyngitis and muscle weakness	All patients achieved TTR stabilization at 8 weeks.

Abbreviations: AE, adverse event; ATTRv, hereditary amyloid transthyretin amyloidosis; EE, efficacy-evaluable; NIS-LL, Neuropathy Impairment Score in the Lower Limbs; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; SAE, serious adverse event; TTR, transthyretin; P-T, Placebo-Tafamidis; T-T, Tafamidis-Tafamidis.

Since, ATTRv-PN is a rare disease, no validated outcome measures were available. Therefore, measures of disease progression with demonstrated sensitivity and specificity in other neuropathies, such as diabetic polyneuropathy, were used. The outcomes measures were Neuropathy Impairment Score in the Lower Limbs (NIS-LL) – a clinical scale that quantifies the motor, sensory and reflex functions in the lower limbs; Norfolk Quality of Life-Diabetic Neuropathy questionnaire (Norfolk QOL-DN) – a 35-item, patient-reported questionnaire that evaluates the impact of sensorimotor and autonomic neuropathy symptoms in the daily life activities; Summated scores from multiple measures of nerve conduction studies, quantitative sensory test (QST) and heart rate response to deep breath (HRDB) – summated 7 nerve testes (Σ7 NTs) assess large-nerve fiber function and summated 3 nerve tests (Σ3 NTSF) assess small nerve fiber function; Modified body mass index (mBMI) as a measure of wasting and autonomic gastrointestinal function –

calculated as the product of BMI and serum albumin; and TTR tetramer stabilization assessed by using a validated immunoturbidimetric assay on patients' plasma samples.[17]

The primary efficacy endpoints at month 18 were analysed on the intent-to-treat (ITT) population (all randomized patients) and included NIS-LL response to treatment (patients were classified as responders if presented an increase from baseline in NIS-LL <2 points) and the least-square mean change from baseline Norfolk QOL-DN total. Patients who discontinued the study due to LT were categorized as NIS-LL nonresponders. The primary endpoints were also analysed in a subgroup of ITT patients who completed the study – efficacy-evaluable (EE) population. This subgroup was pre-specified as it was anticipated that the majority of enrolled patients would be on LT list and undergo LT during the course of the study.[17]

Secondary endpoints used to access tafamidis efficacy included change from baseline at months 6, 12 and 18 in NIS-LL, Norfolk QOL-DN, mBMI, Σ7 NTs and Σ3 NTSFs.

Overall, 128 patients were randomized with similar baseline characteristics between both tafamidis and placebo groups. From this population, 21% discontinued treatment to undergo LT.[17]

In the ITT population at month 18, there was a trend toward more NIS-LL responders in the tafamidis group compared with the placebo group (45.3% versus 29.5%; p=0.068). The least square mean change from baseline Norfolk QOL-DN was not different between both groups at month 18. In the EE population, significantly more patients in the tafamidis group were NIS-LL responders than in the placebo group (60.0% versus 38.1%; p=0.041). The least square mean change from baseline Norfolk QOL-DN was significantly lower in patients treated with tafamidis compared with placebo (0.1 point versus 8.9 points; p=0.045).[17]

Considering the secondary endpoints in the ITT population, tafamidis-treated patients presented less neurologic deterioration at month 18 than placebo patients (NIS-LL change from baseline 2.81 vs 5.83; p=0.027). Nerve function worsened in patients treated with placebo, with 5 times greater mean deterioration in small-fiber function (Σ3 NTSFs; p=0.005) and with no deterioration in large-fiber function (Σ7 NTs; p=0.006). Nerve function was preserved in tafamidis-treated patients. Nutritional status significantly improved in the tafamidis group compared with a mBMI worsening in the placebo group (mBMI change from baseline +39.3 ± 11.5 versus −33.8 ± 11.9, respectively; p<0.00001). TTR stabilization at 18 months was demonstrated in 98% of tafamidis treated patients.[17]

Although a statistical significance in the primary outcomes was not achieved in the ITT population, overall the results suggested a potential role of Tafamidis in slowing neurological progression and improving nutritional status. Several reasons, related to the rarity and complexity of the disease, were discussed to justify these less satisfactory results. The decision to classify patients who underwent LT (21%) as nonresponders, probably also influenced the analysis of NIS-LL in the ITT population.[17]

Fx-006 Study

This 12-month open-label extension study evaluated the long-term efficacy, safety and tolerability of tafamidis in patients who participated and completed the previous study (Fx-005). Patients who were initially randomized to the placebo arm were switched to the active drug arm (placebo–tafamidis group: P-T group) and patients who were in the tafamidis arm continued on tafamidis (tafamidis–tafamidis group: T-T group). The outcome measures were the same as in the Fx-005 trial and evaluated every 6 months. This study enrolled initially 86 patients, from which 63 completed the extension study. A sustained effect of Tafamidis was demonstrated after 30 months of treatment, with no statistically significant difference in the monthly rate change in clinical and neurophysiological measures (NIS-LL, Norfolk QOL-DN, Σ7 NTs and Σ3 NTSFs) between the first 18 months of the previous study and the 12 months of the extension study. Additionally, patients from Fx-005 trial who switched from the placebo arm to the active drug in extension study, also presented slowing of disease progression with significant reduction in the monthly rate of NIS-LL (0.34 in Fx-005 versus 0.16 in Fx-006; p=0.01), improvement in the monthly rate change of Norfolk QOL-DN score (0.61 in Fx-005 versus −0.16 in Fx-006; p<0.001) and amelioration of the nutritional status (mBMI rate of change −1.77 in Fx-005 trial versus 5.19 in Fx-006 trial; p<0.001). Finally, the study also showed that earlier treatment with tafamidis contributed to better outcomes. Patients from the T-T group had slower disease progression compared to patients from the P-T group, in whom tafamidis was initiated later, as evaluated by mean change of NIS-LL from baseline at 30 months (3.0 versus 6.8, respectively; p<0.01) and mean change

of Σ7 NTs from baseline at 30 months (1.6 versus 4.4, respectively; p<0.01). TTR stabilization was obtained in both treatment groups and was superior to 90%.[18]

Fx1A-201 Study

In parallel of Fx-005 study, a Phase II, open-label, single-treatment arm study was conducted in patients with non-Val30Met ATTRv amyloidosis which evaluated the pharmacodynamics, efficacy, and safety of tafamidis in these patients. The study was conducted in two parts. In the first part, patients received tafamidis 20 mg once per day for 6 weeks. At Week 6, blood samples were collected to determine TTR stabilization. If no TTR stabilization was demonstrated at week 6, patients were discontinued from the study. In the second part, all patients demonstrating stabilization at the Week 6 visit continued to receive tafamidis for a total of 12 months. The inclusion criteria were similar to Fx-005 trial, despite excluding patients with Val30Met and Val122Ile mutations. The primary endpoint was TTR stabilization at 6 weeks. The secondary endpoints included TTR stabilization at 6 and 12 months, NIS from both upper and lower limbs, a summated 5 nerve conduction study parameters composite score (Σ5 NCS nds) in order to evaluate large-fiber nerve function, Norfolk-QOL-DN and mBMI. Considering the phenotypical heterogeneity of non-Val30Met mutations with frequent cardiac involvement, cardiac biomarkers, such as Troponin I and N-terminal pro-hormone brain natriuretic peptide (NT-pro-BNP), 12-lead electrocardiogram and echocardiogram parameters were also evaluated throughout the study.

TTR stabilization at Week 6 was achieved in 18 patients from an intent-to-treat population of 19 patients. The one patient (TTR Gly47Ala mutation) who did not demonstrate TTR stabilization was later assessed at 3 and 6 months, achieving then TTR stabilization. After 12 months of treatment, slight neurologic function deterioration was seen with a mean increase of 5.3 in total NIS and mean increase of 0.2 in nerve conduction studies Σ5 NCS nds. Patients with more severe neuropathy (higher baseline NIS) had a greater increase in NIS than patients with milder neuropathy. Nonetheless, there was no significant clinically worsening in the other outcome measures, namely health-related quality of life assessed by Norfolk-QOL-DN, nutritional status (mBMI), cardiac biomarkers and echocardiographic parameters, during the 12 months of treatment.

Fx-1006A Study

This is a Phase III, open-label extension study designed to obtain additional long-term safety and efficacy of tafamidis for treatment of ATTRv amyloidosis patients for up to 10 years or until subjects had access to tafamidis for ATTR-PN via prescription. This study enrolled patients who completed the 18 months placebo-controlled study Fx-005, and then received tafamidis in the 12-month extension study Fx-006, and non-Val30Met patients who received tafamidis in the single-treatment arm study Fx1A-201.[19]

A planned interim analysis (Fx1A-303) was performed to evaluate tafamidis' effect on neuropathy progression and its safety after up to 6 years of treatment.[19] A total of 93 patients were initially enrolled (38 Val30Met ATTRv T-T patients, 37 Val30Met ATTRv P-T patients and 18 non-Val30Met ATTRv patients). At the time of the analysis, 56 (60.2%) had completed the study when tafamidis became available by prescription, 17 remained in the study (18.3%) and 20 had discontinued for several reasons (21.5%). The mean cumulative tafamidis exposure was 5.1 years in the ATTRv Val30Met T-T group, 3.5 years in the ATTRv Val30Met P-T group and 3.6 years in the non-Val30Met ATTRv group. All patients presented in some degree disease progression. ATTRv Val30Met patients who were treated continuously with tafamidis (ATTRv Val30Met T-T group) experienced numerically less neurologic deterioration in NIS-LL and Norfolk QOL-DN than patients who initiated tafamidis 18 months later (ATTRv Val30Met P-T group). A post hoc slope analysis was conducted to compare the rate of neuropathy progression between the T-T and P-T groups. Once patients switched from the placebo arm to the active drug arm (P-T group), the rate of disease progression (NIS-LL and Norfolk QOL-DN) was similar to patients who have been continuously treated with tafamidis (T-T) (Figure 1). Non-Val30Met ATTRv patients, who were older and had more advanced disease, presented neurological function worsening throughout 4 years of treatment. The absence of a comparator in this group hampers the results' interpretation. This study confirmed the long-term efficacy of tafamidis in delaying disease progression and highlighted the importance of early tafamidis treatment to preserve neurological function. Nonetheless, patients who initiated tafamidis later on the disease had still some beneficial effect.[19]

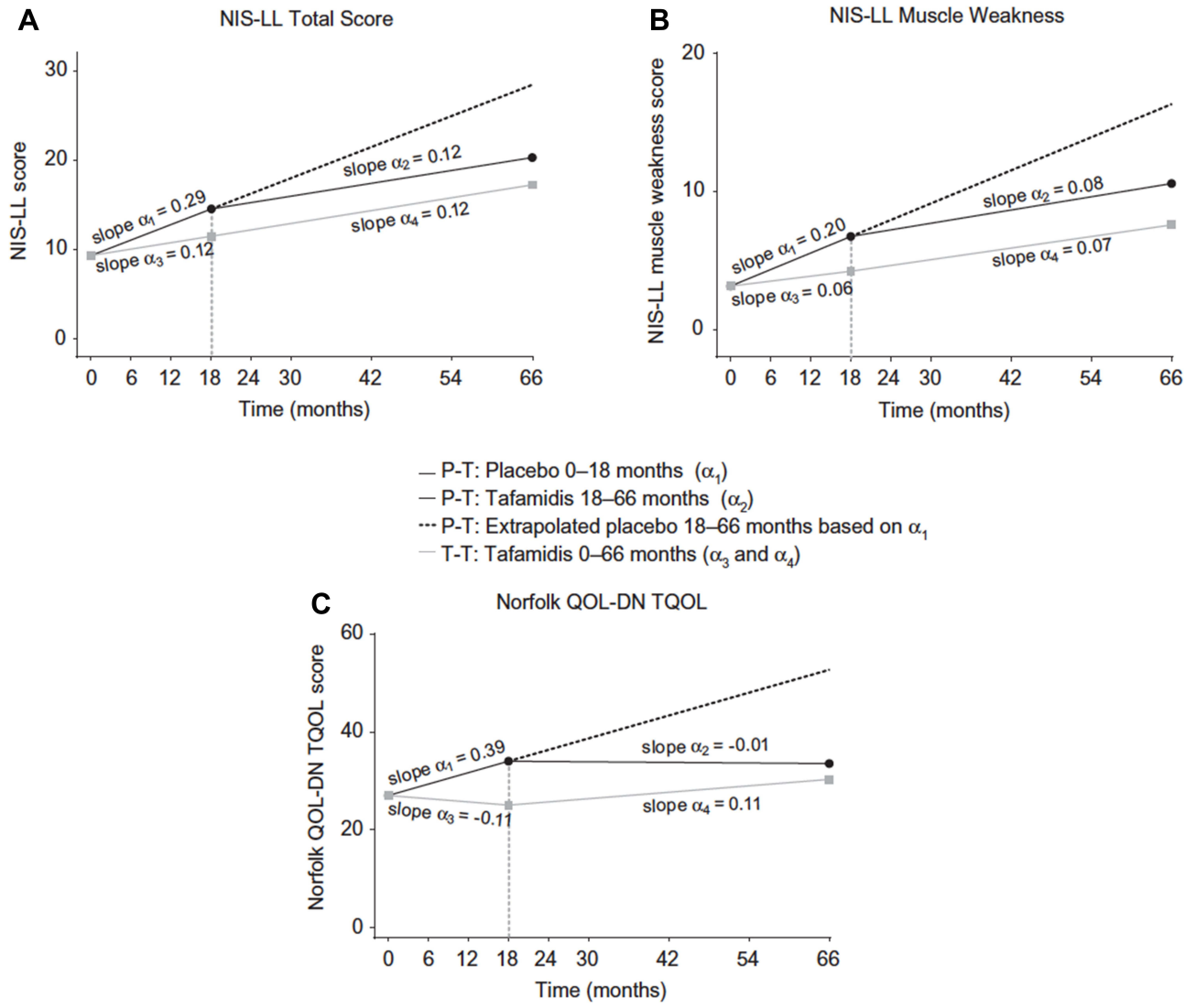

Figure 1 Intent-to-treat slope analysis of (**A**) NIS-LL total score, (**B**) NIS-LL muscle weakness, and (**C**) Norfolk QOL-DN in patients with Val30Met ATTRv-PN (data from Fx-005, Fx-006 and Fx1A-201).[17,18,20] Slopes are adjusted at mean baseline value of the two treatment groups.

Note: Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years" by Fabio A. Barroso, Daniel P. Judge, Ben Ebede, Huihua Li, Michelle Stewart, Leslie Amass & Marla B. Sultan © 2017 The Author(s) taken from Amyloid (2017), Vol 24:3, copyright © Informa UK Limited, trading as Taylor & Francis Group (2017), reprinted by permission of the publisher.[19]

Abbreviations: NIS-LL, Neuropathy Impairment Score in the Lower Limbs; QOL-DN TQOL, Quality of Life-Diabetic Neuropathy total quality of life.

Additionally, in another study a Kaplan–Meyer analysis was performed to evaluate the survival in ATTRv patients enrolled in the Fx-1006A study treated with tafamidis up to 8.5 years.[22] Approximately 85% of Val30Met patients and 75% of non-Val30Met patients were alive at 9 and 8 years, respectively, from the first dose of treatment. Considering the natural history of the disease with a 10-years estimated survival after disease onset in untreated patients, these findings highlight tafamidis treatment beneficial effect on survival in these patients.[22]

Effect of Tafamidis in Japanese Patients

This study was a single-arm, open-label, multicentre study aiming to evaluate TTR stabilization, safety and tolerability, and efficacy in Japanese ATTRv patients with Val30Met and non-Val30Met mutations treated with tafamidis 20 mg once daily. This study included 10 patients (9 Val30Met patients and 1 non-Val30Met patient) aged 20 to 75 years with documented amyloid deposition by biopsy and peripheral neuropathy with Karnofsky Performance Status ≥50. The primary outcome was TTR stabilization at Week 8. The secondary endpoints were change from baseline in NIS score,

Norfolk QOL-DN, neurophysiological tests (Σ7 NTs and Σ3 NTSFs), mBMI and ambulatory status over time. Patients were also classified as responders if there was an increase from baseline in NIS-LL <2.

All patients achieved TTR stabilization at week 8 that was further maintained during the following 18 months. The proportion of NIS-LL responders was 80%, 60% and 40% at 6, 12 and 18 months of follow-up, respectively. The mean NIS-LL change from baseline was 3.3 (NIS-LL at baseline = 17) at 18 months. Although there was a decrease in neurological function, as assessed by NIS, there was stabilization in the neurophysiological studies with preserved mean sural sensory nerve amplitude throughout the study. There was also an improvement of the nutritional status with an mBMI increase at 8 weeks that was maintained during the 18 months of the study. Despite the small population sample and the single-arm design with no placebo comparator, these findings were in agreement with the previous studies, with long-term TTR stabilization and beneficial effect in slowing neuropathy progression and improving nutritional status over 18 months in Japanese patients.[21]

Post Hoc Analysis

Additional post hoc analyses were performed in order to further support the efficacy of tafamidis in slowing disease progression.[23–27]

In one study, baseline-adjusted and multiple imputation analysis of the data from the Fx-005 trial favoured tafamidis over placebo with a lower least squared mean change from baseline in NIS-LL, NIS-LL plus three small nerve fiber tests and NIS-LL plus seven nerve tests at 18 months.[23] Tafamidis effectiveness was also analysed in a subgroup of patients, enrolled in the pivotal trial and its open-label extension studies, with mild neuropathy (NIS ≤ 10) at baseline prior to treatment. Results showed a sustained delay in neurological progression (NIS-LL) and maintenance of nutritional status (mBMI) for up to 5.5 years following early treatment with tafamidis, further supporting the importance of an early diagnosis and treatment initiation.[24] Additionally, another study showed that neurological progression strongly depended on baseline neurologic severity. A linear mixed-effects model for repeated measures was performed using data from the pivotal trial and is open-label extension studies. Patients with lower baseline NIS-LL showed less progression than patients with higher baseline NIS-LL ($p<0.0001$). Furthermore, patients from the T-T group presented slower neurologic progression than patients from the P-T group ($p=0.0088$).[25]

Since gastrointestinal symptoms are common among ATTRv patients, a post hoc analysis evaluated the effect of tafamidis on nutritional status, as assessed by mBMI, in patients enrolled in the 18 month, randomized, placebo-controlled trial and its 12-month open-label extension (Fx-005 and Fx-006). In the 18 months placebo-controlled trial (Fx-005), patients treated with tafamidis had an increased mBMI compared to a decrease in patients from the placebo arm at 18 months. At the end of the open-label extension study (Fx-006), nutritional status significantly improved in patients from both groups (P-T group and T-T group), and the improvement was more pronounced in patients with a lower baseline mBMI.[26]

Finally, another study was conducted in order to better characterize the tafamidis effect on non-Val30Met ATTRv patients. A post hoc analysis compared the baseline-adjusted mean change in NIS-LL in non-VAL30Met patients from the 12-month open-label study (Fx1A-201) versus Val30Met patients at month 12, from the 18-month, double-blind randomized placebo-controlled trial (Fx-005). No difference was seen in the baseline adjusted mean change in NIS-LL at month 12 between non-Val30Met and Val30Met patients treated with tafamidis. This study highlighted the effect of tafamidis on neurological progression was more similar in both genotype groups than previously believed.[27]

Real-World Clinical Experience

Tafamidis efficacy has been further proved in clinical practice setting as published in several studies from endemic and non-endemic areas. Long-term treatment with tafamidis has been effective in slowing neurological progression in early and late-onset patients with distinct phenotypes (neurologic and mixed phenotypes) and in both V30M and non-V30M ATTRv patients.[28–32]

A non-randomized, matched cohort analysis was performed using data from Transthyretin Amyloidosis Outcome Survey (THAOS), the largest observational disease registry of ATTRv-PN patients.[29,30] The study included 252 symptomatic stage I (able to walk without support) ATTRv-PN patients, with TTR documented mutation, treated with

tafamidis over the course of 2 years and further compared to a matched control cohort of untreated patients. Most patients were Val30Met (92.5%) and origin from Portugal (80.2%) where the early-onset phenotype predominates. Over the course of 2 years, tafamidis-treated patients had a significantly lower rate of disease progression compared to control-matched untreated patients, as demonstrated by measures of neurologic function (NIS-LL and nerve conduction studies) and quality of life (Norfolk TQOL). These findings confirmed previous results from clinical trials and provided evidence for the efficacy of tafamidis in clinical practice.[29]

However, smaller and uncontrolled studies with distinct populations reported mixed results.[31,32] Two cohort studies conducted in Italy and France analysed smaller and heterogeneous groups, with later age of onset and the majority of patients carrying non-Val30Met mutations. In both studies, there was a disease progression over time despite tafamidis treatment. However in the Italian study, after the first 6 months of treatment the worsening of neurological function slowed, suggesting there was still a potential benefit of tafamidis treatment in this group of patients.[31] Additionally, in both cohorts, patients presented a more severe neuropathy at baseline, which might explain the less favourable reported outcomes. In fact, late-onset patients and non-Val30Met mutation carriers are associated with higher rates of misdiagnosis and subsequent delayed diagnosis, leading to diagnosis at later stages of the disease.[31,32]

Another retrospective cohort study that included 210 ATTRv patients treated with tafamidis for a maximum follow-up of 66 months calculated a predictive model of response to tafamidis. In this cohort, one-third of patients were classified as responders (NIS change 0 points per year) with complete stabilization of the neurological disease. One-third was classified as non-responders (NIS change 5.9 points per year) with neurological progression similar to untreated patients. The remaining third were defined as partial responders (NIS change 1.8 points per year) with slower overall disease progression and/or improvement in autonomic symptoms and mBMI despite neuropathy progression. Male patients, higher disease severity at baseline and lower level of native TTR at baseline were associated with a lower chance of response to treatment.[33]

In summary, long-term tafamidis treatment has been shown to delay disease progression in ATTRv patients in the clinical practice setting. Some individual factors may influence the response to treatment, being the neuropathy severity at baseline the most evident factor to decrease the likelihood of treatment response. These findings underline the importance of an early diagnosis and prompt treatment in the early stages of the disease and a regular clinical monitoring to assess treatment response.

Tafamidis Safety and Tolerability

Tafamidis 20mg/day was generally safe and well tolerated in ATTRv-PN patients. In the first double-blind, placebo-controlled trial (Fx-005), there were four adverse events (AE) identified: diarrhoea, urinary tract infection, upper abdominal pain and vaginal infection.[17] Since then, patients treated with tafamidis in the open-label extension studies, did not report additional adverse events, even in patients with longer drug exposure.[18,19] All deaths reported in the clinical trials and open-label extension studies were not considered related to tafamidis treatment, but rather related to disease progression or a concurrent medical condition consistent with ATTR amyloidosis.[17–20]

Safety data from the ongoing THAOS, which included 661 patients treated with tafamidis, confirmed tafamidis safety and tolerability with no significant new safety findings in the clinical practice setting.[29,34] A post-marketing surveillance study in Japan also supported previous findings.[35]

There are limited data on the safety of tafamidis during pregnancy. Women of reproductive age are advised to use appropriate contraception while taking tafamidis and for 1 month after stopping treatment.[36] From the 18 reported cases of tafamidis exposure during pregnancy, or 1 month prior to pregnancy either by maternal or father exposure, there was only one case of spontaneous abortion. Furthermore, the outcomes of the pregnancies were as follows: 12 normal newborns, 1 medical termination and 3 with the outcome pending at the time of the reported data.[34]

Although a potential risk of hypersensitivity and hepatic toxicity due to its metabolism by glucuronidation was previously described in nonclinical studies, no hypersensitivity reactions or hepatic events were reported during tafamidis treatment.[36]

Recommendations for Treatment of ATTRv Patients and Tafamidis Role

Tafamidis was the first pharmacological alternative to LT in delaying neuropathy progression in stage I ATTRv patients following its approval in Europe in 2011 and several other countries thereafter.[37,38]

Considering the simplicity of an oral intake, and its proven safety and tolerability, as well as demonstrated efficacy in delaying neuropathy progression in the early stages of the disease, the European Network for ATTR-PN (ATTReuNET) recommends tafamidis as the first-line treatment for stage I ATTR-PN patients, thus replacing LT as standard of care.[39] No controlled trials have been conducted comparing LT and tafamidis for ATTRv-PN patients. Nonetheless, a small study, which compared disease progression in early-stage Val30Met patients, treated with tafamidis or LT, showed similar neurological outcomes in both treatment groups when compared to untreated patients.[40] Additionally, another multicentric hospital-based study in Portugal found that, among early-onset patients, tafamidis was associated with an increased survival compared with LT, probably justified by the considerable risks associated with the surgical procedure and long-term immunosuppression. However, some caution is imperative in interpreting these results, considering the shorter time of follow-up in tafamidis treated patients.[41] Currently, in clinical practice, if disease progression occurs during tafamidis treatment, LT may still be an option for young patients with no contraindications for surgery.[39]

In Japan, tafamidis has been approved in 2013 for any stage ATTRv-PN patients. However, LT remains as the first-line disease-modifying therapy in ATTRv-PN patients. If there is any contra-indication for LT, tafamidis is the drug of choice. Tafamidis is also recommended for patients referred for LT but who are still in the waiting list for a compatible donor.[42]

More recently, gene-silencing drugs have also been approved in Europe for stage 1 and 2 ATTRv-PN patients, considering the robust demonstration of efficacy of these drugs and its relative safety reported in clinical trials.[9,10] In clinical practice, gene-silencing drugs have been prescribed in specific clinical settings, according to patients and their physicians' evaluation of eventual risks and logistic considerations.[43] Gene-silencing drugs have also been approved in the United States of America where tafamidis 20 mg was not approved for ATTRv-PN patient's treatment, considering the absence of robust efficacy in clinical trials.

Finally, an experienced and multidisciplinary team, including a Neurologist and Cardiologist, should regularly and carefully monitor all treated patients in order to assess response to treatment and address any adverse events.[39]

Future Directions and Questions in Management of TTR Amyloidosis Neuropathy

Higher dose of tafamidis (tafamidis 61 mg) was recently approved for hereditary and wild-type transthyretin amyloid patients with cardiomyopathy, after demonstrating reduced all-cause mortality and cardiovascular-related hospitalizations in a multicenter, double-blind, placebo-controlled clinical trial.[44] Since most ATTRv patients may present with a mixed phenotype, it would be interesting to monitor neuropathy progression in patients who are being treated with tafamidis 61 mg due to cardiac involvement. It has been speculated that ATTRv-PN patients classified as non-responders or partial responders to tafamidis 20mg, may benefit from higher doses of TTR stabilizer.[32] Clinical data regarding neuropathy progression in patients treated with tafamidis 61 mg are yet to be published.

It is increasingly recognized that an early diagnosis is crucial for delaying disease progression and improving its prognosis. The diagnostic delay is still significant, especially in non-endemic countries and in late-onset and sporadic cases. Several recommendations and red flags have been published to increase awareness and improve diagnosis of these patients.[45,46] Additionally, some research has been conducted in order to identify disease biomarkers that might assist in the earliest detection of the disease. To date, no treatment has been approved for asymptomatic carriers. Regular monitoring of asymptomatic carriers, especially during the previous years of the predicted age of onset, is crucial for the early detection of the disease.[47]

Another question of interest is the effect of tafamidis on patients submitted to LT. First, in patients who are recipient of a domino LT and may develop some years later amyloidotic neuropathy.[48] To date, no treatment has been available for treatment of acquired TTR amyloidosis in this group of patients. Nonetheless, it seems logical that the use of a TTR stabilizer may play a role in preventing neuropathy development. Second, ATTRv patients who are submitted to LT may

still develop neuropathy progression.[49] Probably, combined treatment of LT and TTR stabilizer could improve neurological outcomes. However, no data to support this combined approach has been published. Finally, some ATTRv patients, including Val30Met patients submitted to LT, may develop ocular and central nervous system (CNS) manifestations due to TTR production in the eye in the choroid plexus.[50,51] Although levels of tafamidis could be detected in the cerebral spinal fluid (CSF) and vitreous body in patients treated with tafamidis 20 mg, suggesting that tafamidis could cross the blood-brain and blood-eye barriers,[52] no efficacy of tafamidis in preventing or delaying ocular and CNS involvement has been demonstrated.[53]

Conclusion

Tafamidis is an effective, safe and well-tolerated pharmacological therapy for ATTRv-PN patients in early stages of the disease (stage 1). Based on clinical trials and its extension-studies and around 10 years of experience in the clinical practice setting, tafamidis remains a valuable option in the treatment of early-stage ATTRv-PN.

Abbreviations

ATTReuNet, European Network for ATTR-PN; ATTRv, hereditary amyloid transthyretin (ATTRv) amyloidosis; ATTRv-PN, hereditary amyloid transthyretin amyloidosis with polyneuropathy; CNS, central nervous system; CSF, cerebrospinal fluid; EE, efficacy-evaluable; FAP, familial amyloid polyneuropathy; HRDB, Hear rate deep breathing; ITT, intent to treat; LT, liver transplantation; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; NIS-LL, Neuropathy Impairment Score in the Lower Limbs; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NYHA, New York Heart Association; P-T, placebo-tafamidis; QST, quantitative sensory test; RNA, ribonucleic acid; THAOS, Transthyretin Amyloidosis Outcome Survey; T-T, tafamidis–tafamidis; TTR, transthyretin; Σ3 NTSF, summated 3 nerve tests that assess small fiber function; Σ5 NCS nds, summated 5 nerve conduction study parameters composite score; Σ7 NTs, summated 7 nerve tests that assess large fiber function.

Disclosure

The authors report no conflicts of interest in this work.

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