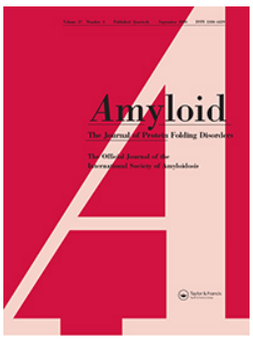

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ARTICLE

Quality of life outcomes in APOLLO, the phase 3 trial of the RNAi therapeutic patisiran in patients with hereditary transthyretin-mediated amyloidosis

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ABSTRACT

Introduction: Hereditary transthyretin-mediated (hATTR) amyloidosis is a rare, fatal, multisystem disease leading to deteriorating quality of life (QOL). The impact of patisiran on QOL in patients with hATTR amyloidosis with polyneuropathy from the phase 3 APOLLO study (NCT01960348) is evaluated.

Methods: Patients received either patisiran 0.3 mg/kg ($n = 148$) or placebo ($n = 77$) intravenously once every three weeks for 18 months. Multiple measures were used to assess varying aspects of QOL.

Results: At 18 months, compared with placebo, patisiran improved Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score; (least squares [LS] mean difference: −21.1; $p = 1.10 \times 10^{-10}$; improved across all domains), EuroQoL 5-dimensions 5-levels (LS mean difference: 0.2; $p = 1.4 \times 10^{-12}$), EuroQoL-visual analog scale (LS mean difference: 9.5; p=.0004), Rasch-built Overall Disability Scale (LS mean difference: 9.0; $p = 4.07 \times 10^{-16}$) and Composite Autonomic Symptom Score-31(COMPASS-31; LS mean difference: −7.5; p=.0008). Placebo-treated patients experienced rapid QOL deterioration; treatment effects for patisiran were observed as early as 9 months. At 18 months, patisiran improved Norfolk QOL-DN total score and three individual domains as well as COMPASS-31 total scores relative to baseline. Consistent benefits were also observed in the cardiac subpopulation.

Conclusion: The benefits of patisiran across all QOL measures and the rapid deterioration observed with placebo, highlight the urgency in early treatment for patients with hATTR amyloidosis with polyneuropathy.

Abbreviations: ADL: activities of daily living; ATTR: transthyretin-mediated; CI: confidence interval; COMPASS-31: Composite Autonomic Symptom Score-31; EQ-5D-5L: EuroQoL 5-dimensions 5-levels; EQ-VAS: EuroQoL-visual analogue scale; FAP: familial amyloid polyneuropathy; GI: gastrointestinal; hATTR: hereditary transthyretin-mediated; LS: least squares; NIS: Neuropathy Impairment Score; Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy; PND: polyneuropathy disability; QOL: quality of life; R-ODS: Rasch-built Overall Disability Scale; RNAi: RNA interference; SD: standard deviation; SEM: standard error of the mean; THAOS: Transthyretin Amyloidosis Outcomes Survey; TTR: transthyretin

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APOLLO; hereditary transthyretin-mediated amyloidosis; patisiran; quality of life; Norfolk QOL-DN

Introduction

Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is a rare, inherited, progressively debilitating and fatal disease caused by mutations in the transthyretin (*TTR*) gene [1–8]. This multisystem disease has a range of manifestations, which includes peripheral sensory/motor neuropathy, autonomic neuropathy and/or cardiomyopathy [2–4,9,10]; the majority of patients develop a mixed phenotype with both polyneuropathy and cardiomyopathy [11–14]. Predominant symptomatology can

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Supplemental data for this article is available online at here.

differ between patients, even among those with the same mutation, however, each mutation has been associated with multisystem involvement [12]. Initial presentation of hATTR amyloidosis commonly includes neuropathy, gastrointestinal (GI) disturbances and/or other autonomic dysfunction with little impairment of mobility (familial amyloid polyneuropathy [FAP] stage 1; polyneuropathy disability [PND] score I and II). With worsening disease, patients experience increasing motor weakness, loss of touch and temperature sensation, and reduced mobility resulting in the need for a walking device (e.g. a cane) (FAP stage 2; PND score IIIa/IIIb). Generalized weakness, cachexia and incontinence confine patients to a wheelchair or bed in the late stages of disease (FAP stage 3; PND score IV) [15–17]. The disease is associated with a poor prognosis, with an overall median survival of 4.7 years following diagnosis [18] that is further reduced to 3.4 years for patients with cardiac manifestations [19].

Due to the multiple organ and tissue involvement [8], progressive increase in symptom frequency and/or severity and worsening disability has a detrimental effect on patient quality of life (QOL) and leads to loss of physical function. This subsequently impacts the patients' abilities to complete everyday tasks, work and attend social functions. Among the disease symptoms, neuropathy manifests as pain, sensation loss, weakness and reduced mobility, and can significantly impair patients' abilities to perform activities of daily living such as buttoning a shirt or turning a key in a lock [20]. Autonomic dysfunction leads to orthostatic intolerance and debilitating GI symptoms that are associated with loss of consciousness and extreme constipation and diarrhea, respectively. Incontinence resulting from GI manifestations and autonomic dysfunction has been shown to impede a patient's ability to participate in day-to-day activities [21,22]. The presence of cardiomyopathy can result in shortness of breath, edema and palpitations [12,23–26], leading to a progressive decline in physical functioning over time and burden on the patient [27,28]. Furthermore, patient perspective studies highlight the impact of hATTR amyloidosis on anxiety/depression and social interactions [21]. As a result of the impact of disease symptoms, patients with hATTR amyloidosis commonly have high healthcare resource utilization and are increasingly dependent on caregivers in their daily lives [29–31]. This multifaceted and multisystem impairment in patients with hATTR amyloidosis thus severely affects physical, psychological and social functioning, and contributes to the overall worsening in QOL observed in these patients compared with the general population [25,32,33].

As hATTR amyloidosis affects QOL in a multitude of ways, many factors should be considered to understand the full impact of this complex disease. Several clinical studies of treatments for hATTR amyloidosis have included QOL as a key efficacy endpoint [13,34,35], indicating the importance of QOL in assessing the benefit of therapies for this disease. However, there is currently no single, standardized instrument that is designed to measure all aspects of QOL in hATTR amyloidosis. To fully capture the multisystem complexities of hATTR amyloidosis on patient lives, multiple QOL measures – the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire, EuroQoL 5-dimensions 5-levels (EQ-5D-5L) questionnaire, EuroQoL visual analog scale (EQ-VAS), Rasch-built Overall Disability Scale (R-ODS) and Composite Autonomic Symptom Score-31 (COMPASS-31) questionnaire – were examined in the phase 3 APOLLO study of patisiran [16]. Patisiran is an RNA interference (RNAi) therapeutic that targets hepatic production of mutant and wild-type *TTR* [36,37], and has been approved in several countries globally for the treatment of hATTR amyloidosis with polyneuropathy [38,39]. The objective of this analysis was to describe the effect and impact of patisiran on QOL in patients with hATTR amyloidosis with polyneuropathy from the APOLLO study.

Materials and methods

The full methodology and study design details for APOLLO have been described previously [14,16], and relevant details are summarized briefly below. All QOL measures described here were included as secondary (Norfolk QOL-DN, R-ODS, and COMPASS-31) or exploratory (EQ-5D-5L and EQ-VAS) endpoints in the APOLLO study.

Study design and patients

APOLLO (NCT01960348) was a multicenter, international, randomised, double-blinded, placebo-controlled and a phase 3 study. The protocol was approved by central and local institutional review boards or ethics committees and conducted in accordance with the International Conference on Harmonization for Good Clinical Practice, the Declaration of Helsinki, and the 1996 Health Insurance Portability and Accountability Act. Patients were enrolled at 44 sites across 19 countries between December 2013 and January 2016. Eligible patients were aged 18 – 85 years old with a documented *TTR* mutation and diagnosis of hATTR amyloidosis, polyneuropathy (Neuropathy Impairment Score [NIS]: 5–130), adequate liver and kidney function, and PND score $\leq$ IIIb. A cardiac subpopulation was pre-defined and included patients with a baseline left ventricular wall thickness $\geq$13 mm and no history of aortic valve disease or hypertension.

Assessments

Primary efficacy and safety

Full details of the primary efficacy and safety results of patisiran in the overall APOLLO population and in the cardiac subpopulation have been described previously [14,40].

Measures of overall QOL: Norfolk QOL-DN and EuroQoL questionnaires

Norfolk QOL-DN

The Norfolk QOL-DN was designed to assess the patients' perceptions of symptoms associated with nerve fiber damage

in diabetic neuropathy. It has been validated in populations with mild-to-severe forms of diabetic neuropathy [41–43] and has been demonstrated to be a reliable indicator of disease severity in hATTR amyloidosis with polyneuropathy [32]. The 35-item Norfolk QOL-DN questionnaire used in the APOLLO study comprises five domains (activities of daily living [score range: 0–20], physical functioning/large-fiber neuropathy [−4 to 56], small-fiber neuropathy [0–16], autonomic neuropathy [0–12] and symptoms [0–32]; total range −4 to 136), with a higher score indicating worsening impairment [16,32].

EQ-5D-5L

EQ-5D-5L is a patient-reported, standardized five-dimension instrument for use as a measure of health outcomes [44]. It is considered applicable to a wide range of health conditions and treatments and has been utilized as a measure of QOL in the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry, which collects data on the natural history of transthyretin-mediated (ATTR) amyloidosis [12]. The five dimensions include mobility, self-care (focus on washing and dressing oneself), usual activities (prompts include work, housework, leisure activities, etc.), pain/discomfort and anxiety/depression, each with five levels of severity (no problems, slight problems, moderate problems, severe problems and extreme problems). The patients indicate their health state by choosing the most appropriate statement in each of the five dimensions. This results in a one-digit number expressing the level selected for that dimension. The digits for five dimensions can be combined in a five-digit number describing the respondent's health state. It should be noted that the numerals 1–5 have no arithmetic properties and should not be used as a cardinal score. The health EQ-5D-5L health states are converted from each dimension score to a single index value between 0 (worst health) and 1 (best health).

EQ-VAS

EQ-VAS is a self-reported measure of overall health that records a respondent's self-rated health at the time of assessment (indicates how the person's health is 'today' only; range 0–100) with endpoints listed as 'the best health you can imagine' (100) and 'the worst health you can imagine' (0) [44].

Measure of QOL related to activities of daily living: R-ODS

R-ODS measures activities of daily living and captures the ability of an individual to function independently in daily life [20,45]. The 24-item R-ODS measures limitations in usual daily activities and social participation [16,29,46]. Activities range from the ability to read a newspaper or book to the ability to run. Other activities include brushing teeth, going to the toilet, turning a key in a lock, and bending and picking up an object. Each of the items is assigned a score of 0 (unable to perform), 1 (able to perform, but with difficulty) or 2 (able to perform without any difficulty) by the patient [46]. If a patient cannot do the activity without the help of others or without using special equipment, they are instructed to mark 'able to perform, but with difficulty'. Patients are instructed to respond to the questions based on how they *usually* can perform the activity. A decrease in overall R-ODS score reflects worsening disability [16,46].

Measures of QOL related to autonomic dysfunction: COMPASS-31

COMPASS-31 is a 31-question patient-reported outcome assessment, which measures autonomic symptoms across six weighted domains (orthostatic intolerance [40 points]; vasomotor [5 points]; secretomotor [15 points]; GI [25 points]; bladder [10 points]; and pupillomotor [5 points]), on a 100-point scale [47]. Weights for each domain are determined based on perception of importance of the domain in contributing to autonomic symptoms [47]. A higher score indicates a worsening of autonomic neuropathy symptoms [14,16,47].

Statistical analysis

Full details of the statistical analyses have been described previously [14,16]. Efficacy analyses were based on the modified intention-to-treat (mITT) population (all randomized patients who received ≥1 dose of study drug). Norfolk QOL-DN, R-ODS, COMPASS-31, EQ-5D-5L, and EQ-VAS were assessed using a mixed-effects model for repeated measures. For EQ-5D-5L, a categoric summary of the numbers and percentages of patients reporting each ordinal response within each dimension was collected.

Results

APOLLO trial population

A total of 225 patients were randomized to receive patisiran ($n = 148$; 138 [93.2%] completed the trial) or placebo ($n = 77$; 55 [71.4%] completed the trial). The two groups were generally balanced with respect to baseline characteristics and disease severity as detailed in Adams et al. [14]. Overall, 126 patients (56.0%) were included in the pre-defined cardiac subpopulation, with a higher percentage in the patisiran group (90/148 [60.8%]) compared with the placebo group (36/77 [46.8%]). Baseline characteristics of the pre-defined cardiac subpopulation (defined as a baseline left ventricular wall thickness ≥13 mm and no history of aortic valve disease or hypertension) are provided in Solomon et al. [40]. Baseline QOL measurements for the overall APOLLO study population are detailed in Supplementary Table S1. These measures are also well balanced between treatment groups and indicate the notable QOL impairment at baseline in patients enrolled in APOLLO.

Measures of overall QOL: Norfolk QOL-DN and EuroQoL questionnaires

Norfolk QOL-DN

At baseline, the mean (standard deviation [SD]) total Norfolk QOL-DN score was 59.6 (28.2) and 55.5 (24.3) in

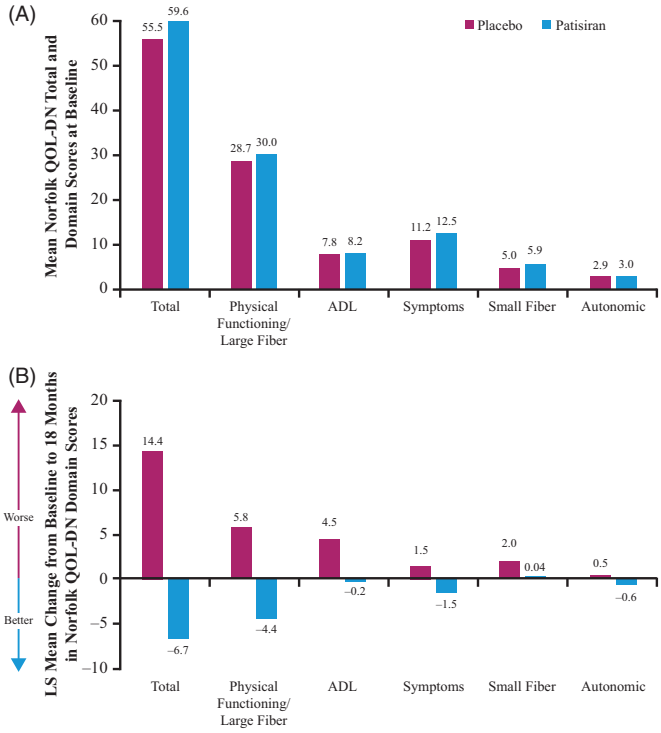

Figure 1. Norfolk QOL-DN assessments in the APOLLO study. (A) Mean Norfolk QOL-DN total and domain scores at baseline in APOLLO patients receiving patisiran or placebo. (B) LS mean change in total and in individual Norfolk QOL-DN components (ranges: activities of daily living, 0–20; physical functioning/large-fiber neuropathy, −4 to 56 small-fiber neuropathy, 0–16; autonomic neuropathy, 0–12; symptoms, 0–32; total range −4 to 136, with a higher score indicating greater impairment) from baseline to Month 18 in patients receiving patisiran or placebo. ADL: activities of daily living; LS: least squares; Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy questionnaire.

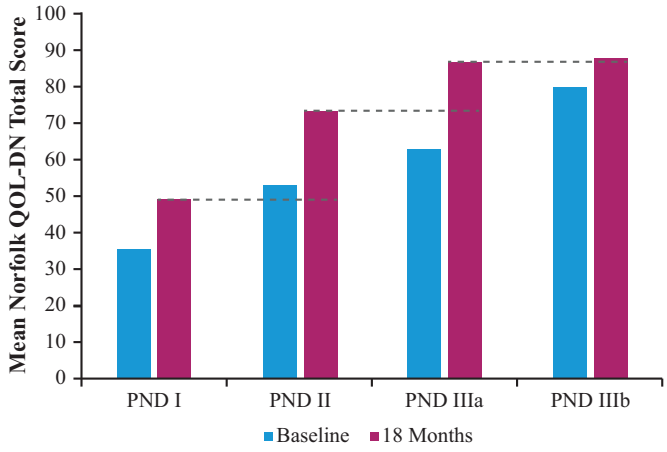

Figure 2. Mean total Norfolk QOL-DN score at baseline and after 18 months in APOLLO patients receiving placebo stratified according to baseline PND score. Dotted lines indicate the level of deterioration of Norfolk QOL-DN in each successive disease stage (PND score) in the placebo-treated patients after 18 months. Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PND: polyneuropathy disability.

the patisiran and placebo groups, respectively (Supplementary Table S1 and Figure 1(A)). Baseline scores across all individual Norfolk QOL-DN domains are shown in Figure 1(A). The total Norfolk QOL-DN score at baseline in APOLLO was related to disease stage, with patients with worse PND scores (PND IIIa/b) reporting higher Norfolk QOL-DN scores (worse QOL), as well as demonstrating rapid deterioration over the 18 months across all disease stages (Figure 2).

As previously characterized [14], after 18 months of treatment in APOLLO there was a significant improvement from baseline in total Norfolk QOL-DN score in the patisiran group compared with the placebo group, with a difference in least squares (LS) mean change from baseline of −21.1 points (95% confidence interval [CI]: −27.2, −15.0; $p = 1.10 \times 10^{-10}$). A difference between treatment groups was evident at the first assessment at 9 months (LS mean change from baseline in total score was −7.5 and +7.5 in the patisiran and placebo groups, respectively) [14]. Over 18 months, LS mean total Norfolk QOL-DN scores improved relative to baseline in the patisiran group but rapidly deteriorated in the placebo group [14]. At 18 months, 51.4% of the patients who received patisiran had an improvement (<0 change from baseline to 18 months) in the Norfolk QOL-DN score, compared with 10.4% of those who received placebo, equating to a 10 odds ratio (95% CI: 4.4, 22.5) of improvement for patisiran versus placebo.

An analysis of the LS mean change from baseline to 18 months in individual Norfolk QOL-DN domain scores also favored patisiran compared with placebo across all five domains (Figure 1(B)). By 18 months, the greatest differences between the patisiran and placebo groups were seen in the domains of physical functioning/large-fiber neuropathy (LS mean difference in change from baseline at 18 months: −10.2; 95% CI: −13.7, −6.8) and activities of daily living (LS mean difference: −4.7; 95% CI: −6.0, −3.5). The physical functioning/large-fiber, symptoms, and autonomic neuropathy domains also improved relative to baseline with patisiran treatment (LS mean change from baseline to 18 months of −4.4, −1.5 and −0.6, respectively). In patisiran-treated patients, analysis of Norfolk QOL-DN symptom domain questions (deep pain, electric shocks, numbness, superficial pain, tingling/pins and needles, weakness and other unusual sensations) demonstrated improvement from baseline at 18 months for each domain at the majority of sites assessed (hands, arms, feet, and legs; Figure 3(A)). In contrast, placebo-treated patients reported a worsening from baseline for each symptom domain across the majority of body parts assessed (Figure 3(B)). In a further *post-hoc* analysis of the Norfolk QOL-DN assessment, Pearson correlations of change in score at 18 months in the mITT population demonstrated moderate to strong correlations of total Norfolk QOL-DN score with all other QOL measures assessed (R-ODS, $r = -0.69$; COMPASS-31, $r = 0.48$; EQ-5D-5L, $r = -0.61$ and EQ-VAS, $r = -0.47$).

EQ-5D-5L

The mean (SD) EQ-5D-5L scores at baseline were similar in the patisiran and placebo groups (0.6 [0.2] each; Supplementary Table S1). At 18 months, patients receiving patisiran treatment had an improved EQ-5D-5L score compared with those receiving placebo (LS mean difference:

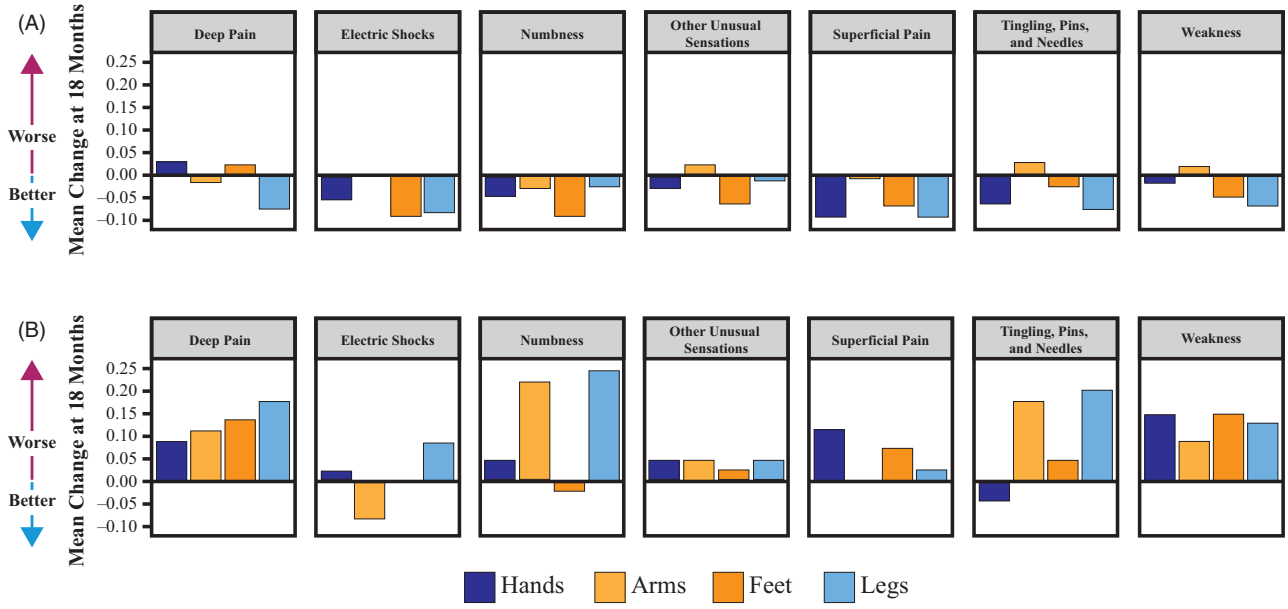

Figure 3. Mean change from baseline at 18 months in Norfolk QOL-DN symptom domain questions in (A) patisiran-treated or (B) placebo-treated patients. Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy questionnaire.

+0.2 points; 95% CI: 0.15, 0.25; $p = 1.4 \times 10^{-12}$; Figure 4(A)). A difference between treatment groups in favor of patisiran was also evident at the first assessment at 9 months (LS mean difference between groups: +0.1 points; 95% CI: 0.05, 0.14). In a *post-hoc* analysis, a larger proportion of patisiran-treated patients demonstrated preservation or improvement (≤0 point change from baseline to 18 months) in each EQ-5D-5L dimension compared with patients receiving placebo (mobility: 69.5 vs. 22.1%; self-care: 66.2 vs. 20.8%; usual activities: 71.7 vs. 24.7%; pain/discomfort: 73 vs. 31.2%; anxiety/depression: 81.1 vs. 45.5%, respectively).

EQ-VAS

The mean (SD) baseline EQ-VAS scores were 55.7 (20.0) and 54.6 (18.0) for the patisiran and placebo groups, respectively (Supplementary Table S1). EQ-VAS score improved (LS mean change: +2.4 points) in patisiran-treated patients and worsened (LS mean change: −7.1 points) in patients receiving placebo, resulting in a LS mean difference of +9.5 points in favor of patisiran at 18 months (p=.0004; Figure 4(B)). Based on the EQ-VAS scores, patisiran-treated patients experienced a benefit in their overall health status, whereas patients receiving placebo perceived a rapid decline in their overall health within the 18 months of the APOLLO trial.

Measure of QOL related to activities of daily living: R-ODS

At baseline, the frequency distribution of R-ODS responses in patients in the placebo and patisiran groups of the APOLLO study indicated substantial difficulty in performing the major everyday activities (Figure 5(A)). Patients reported some difficulty in performing lower-intensity tasks, such as reading a book or newspaper (26.7%) and eating (30.2%) whereas most patients were unable to perform more difficult tasks such as standing for a long period of time (62.7%) or running (75.6%). At 18 months, the overall R-ODS score indicated a significant benefit for patisiran versus placebo, with a difference in LS mean change from baseline of +9 (standard error of the mean [SEM] 1.0; 95% CI: 7.0, 10.9; $p = 4.07 \times 10^{-16}$; Figure 5(B)). The LS mean change from baseline to 18 months was 0 in the patisiran group, compared with −8.9 in the placebo group (Figure 5(B)). A difference between treatment groups was also evident at 9 months (LS mean difference: +4.3 points; 95% CI: 2.7, 5.8; Figure 5(B)).

At 18 months, the proportion of patients unable to perform activities was lower in the patisiran group compared with the placebo group in most activities assessed (Figure 5(A)), including high-intensity activities such as taking a shower (8.7 vs. 24.1%) and walking one flight of stairs (24.6 vs. 48.1%). A higher proportion of placebo-treated patients than patisiran-treated patients were unable to perform even low-intensity activities, such as making a sandwich (37 vs. 10.1%) or turning a key in a lock (27.8 vs. 10.1%), after 18 months of treatment. Patisiran treatment also led to an increase in the number of patients that found some everyday tasks possible, with either some or no difficulty, compared with placebo-treated patients following 18 months. Such tasks included walking one flight of stairs (able with some difficulty, 50 vs. 42.6%; able with no difficulty, 25.4 vs. 9.3%) and bending to pick up an object (able with some difficulty, 50 vs. 38.9%; able with no difficulty, 29 vs. 16.7%, respectively).

Measure of QOL related to autonomic dysfunction: COMPASS-31

The mean (SD) COMPASS-31 score at baseline was 30.6 (17.6) and 30.3 (16.4) points in the patisiran and placebo group, respectively (Supplementary Table S1). Patisiran-treated patients had a significantly greater reduction in autonomic function score from baseline to 18 months than

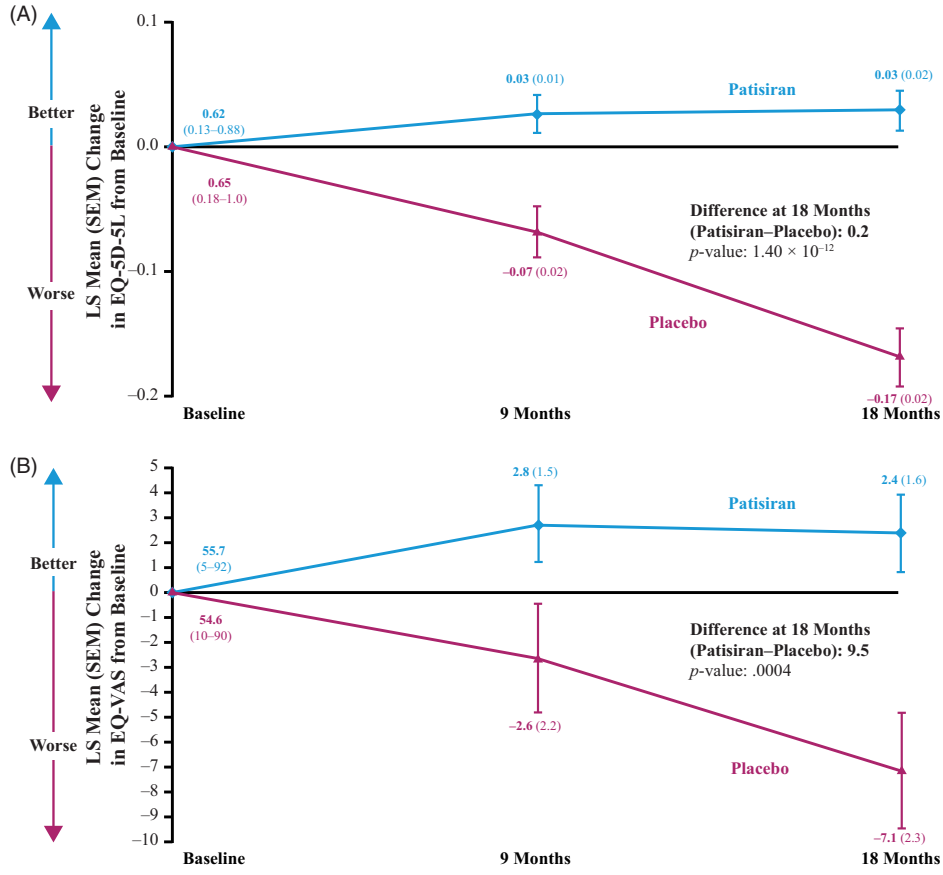

Figure 4. EQ-5D-5L and EQ-VAS assessments in the APOLLO study in the mITT population. (A) LS mean change in EQ-5D-5L score (range: 0 [worst health] to 1 [no impairment]) from baseline to 18 months in placebo and patisiran groups. (B) LS mean change in EQ-VAS score (range: 1–100) from baseline to 18 months in placebo and patisiran groups. At baseline, mean (range) scores for patisiran and placebo groups are shown on the graph. EQ-5D-5L: EuroQoL 5-dimensions-5 levels questionnaire; EQ-VAS: EuroQoL visual analog scale questionnaire; LS: least squares; mITT: modified intention-to-treat; SEM: standard error of the mean.

patients receiving placebo (LS mean difference: −7.5; 95% CI: −11.9, −3.2; p=.0008). This improvement from baseline in patisiran-treated patients was observed across all individual domains of COMPASS-31 [48].

Cardiac subpopulation

Consistent with the overall APOLLO population, patisiran-treated patients in the pre-defined cardiac subpopulation experienced an improvement in QOL over 18 months compared with placebo. The mean change from baseline at 18 months in Norfolk QOL-DN in the patisiran and placebo groups was −2.6 and +20.4, respectively (LS mean difference: −23.0; 95% CI: −31.9, −14.0). In patients receiving patisiran, the physical functioning/large-fiber neuropathy, symptoms and autonomic domains all improved compared with baseline at 18 months, and all domains improved compared with placebo at 18 months. All domains worsened in patients receiving placebo compared with baseline at 18 months. When evaluating EQ-5D-5L in the cardiac subpopulation, there was a mean change from baseline to 18 months of −0.02 and −0.28 in the patisiran and placebo groups, respectively (LS mean difference: 0.26; 95% CI: 0.19, 0.34). In the cardiac subpopulation, the R-ODS mean change from baseline at 18 months in the patisiran and placebo groups was −1.9 and −11.8, respectively (LS mean difference: 9.9; 95% CI: 6.7, 13.0). The difference in R-ODS score between the patisiran and placebo groups at 18 months was slightly greater than that seen in the overall APOLLO population. For COMPASS-31, patisiran-treated patients in the cardiac subpopulation experienced an improvement from baseline to 18 months (mean change: −4.3 points; 95% CI: −7.5, −1.2); conversely, patients receiving placebo in the cardiac subpopulation experienced a decline in autonomic function (mean change: +4.6 points; 95% CI: −0.7, 9.9; LS mean difference patisiran–placebo: −9; 95% CI: −15.0, −2.9).

Discussion

hATTR amyloidosis has a heterogeneous presentation, in which polyneuropathy, autonomic dysfunction and cardiac involvement most often coexist and result in a wide range of signs and symptoms that reduce QOL [3,4,20–22,25,49–51].

The debilitating impact of this disease is highlighted by baseline scores in all QOL measures assessed in the APOLLO study, that were consistently worse in patients with hATTR amyloidosis compared with healthy adult volunteers [32,52–54]. In particular, APOLLO patients

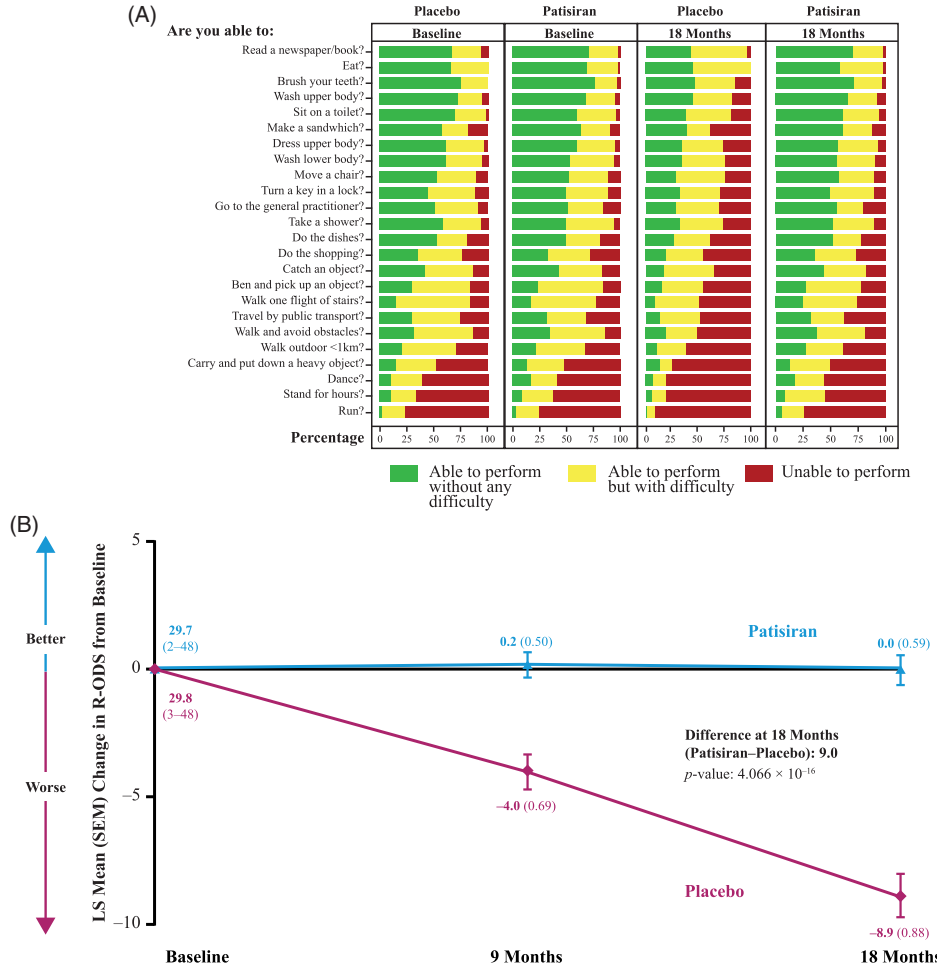

Figure 5. R-ODS assessments in the APOLLO study. (A) R-ODS responses at baseline and at 18 months in the overall APOLLO study population in patients receiving patisiran or placebo. Percentage of patients able to perform a task without any difficulty, able to perform a task but with some difficulty and unable to perform a task are shown for each treatment group at baseline and at 18 months. (B) LS mean change from baseline in overall R-ODS from baseline to 18 months in patients receiving patisiran or placebo. At baseline, mean (range) scores for patisiran and placebo groups are shown on the graph. LS: least squares; R-ODS: Rasch-built Overall Disability Scale; SEM: standard error of the mean.

experienced worse baseline scores in total and in each individual domain of Norfolk QOL-DN (Figure 1(A)) than healthy volunteers (total: 2.6 points) [32]. Furthermore, worse baseline scores than healthy volunteers were observed in EQ-5D-5L (0.9 in healthy volunteers [53]) and EQ-VAS (≥71.6 in healthy population (Supplementary Table 1) [54]). The mean baseline COMPASS-31 scores also indicated substantial autonomic impairment compared with a score of approximately 9 points reported in healthy volunteers [52].

The burden on QOL is also significantly worse in patients with hATTR amyloidosis compared with other diseases [53]. Consistent with a recent analysis using baseline data from the phase 3 NEURO-TTR study of inotersen [55], in the APOLLO study (Supplementary Table 1), baseline Norfolk QOL-DN total scores and the domain of activities of daily living scores were worse than that reported by Veresui et al. [56] for patients with self-reported diabetic neuropathy with at least one episode of ulceration, gangrene, or amputation (total score 50.4 and domain score 5.9, respectively). Baseline data from the NEURO-TTR study also indicated that the impairment in physical functioning in patients with hATTR amyloidosis was comparable with or worse than, other chronic conditions (e.g. chronic heart failure, Crohn's disease) [55], while baseline EQ-5D-5L scores show hATTR amyloidosis is associated with greater impairment in QOL than reported in cancer and heart disease [53]. All together, these findings highlight the tremendous impact of hATTR amyloidosis and the need for early diagnosis and effective early treatment to improve outcomes.

In the current analysis of phase 3 APOLLO data, patisiran treatment demonstrated a significant benefit compared with placebo across all measures of QOL, providing evidence of the efficacy of this drug on the wide spectrum of manifestations that dramatically affect daily functioning and social life for patients with hATTR amyloidosis. The improvements in Norfolk QOL-DN score at 18 months strongly correlated with improvements in R-ODS and EQ-5D-5L and had a moderate positive correlation with improvements in COMPASS-31 and EQ-VAS. This highlights that QOL tools used in APOLLO were appropriate measures for this disease and further strengthens the significant data demonstrating the efficacy of patisiran on other

outcome measures. Compared with placebo, differences in favour of patisiran were frequently demonstrated after 9 months of treatment, with statistically significant improvement across all QOL measures at 18 months. This improvement was also observed in the pre-defined cardiac subpopulation in APOLLO, highlighting the benefit of patisiran on QOL for patients with the commonly observed mixed phenotype of polyneuropathy and cardiomyopathy. This latter finding is of considerable importance given the substantial QOL impairment associated with cardiomyopathy in these patients [18,50]. Of note, the outcomes for EQ-5D-5L, R-ODS, and COMPASS-31 were comparable with those reported in the phase 2 OLE study, broadening the evidence supporting the benefit of patisiran treatment on QOL in patients with hATTR amyloidosis [57].

This study also highlights the rapid deterioration in QOL experienced by patients with hATTR amyloidosis, as demonstrated by the consistently progressive worsening across QOL endpoints in placebo patients in the overall population and cardiac subpopulation. Overall, the rapid disease worsening in patients who received placebo in the APOLLO study is aligned with the natural history studies of the disease, which describe progressive worsening of QOL measures in patients with neurologic involvement [1] or cardiac involvement [50]. The worsening of hATTR amyloidosis is particularly noticeable when compared with other diseases, including different polyneuropathies. For example, natural history and placebo-controlled interventional studies in patients with hATTR amyloidosis with polyneuropathy show a 10- to 14-point increase (worsening) per year in neurologic impairment as measured by the NIS [1], compared with NIS progression at a rate that is typically less than 1 point per year in patients with diabetic polyneuropathy [58]. Considering the significant correlation between NIS score and QOL scores (e.g. Norfolk QOL-DN and SF-36) in patients with hATTR amyloidosis [32,59], these data suggest a more rapid decline in QOL in this disease compared with diabetic polyneuropathy.

The findings of the current study highlight the urgency to diagnose patients as early as possible, and subsequently, start treatment. In patients randomized to the placebo group in APOLLO, the most profound worsening in QOL occurred in the earlier stages of disease (Figure 2), with patients continuing to accumulate greater QOL burden with each PND score increase. Within 18 months, patients on placebo with a PND score of II or IIIa at baseline experienced a decline in Norfolk QOL-DN score that surpassed the mean baseline Norfolk QOL-DN score for patients with PND IIIa or IIIb at baseline, respectively. Consistently, the importance of early intervention in hATTR amyloidosis is suggested by an observational study in untreated patients indicating a steep decline in Norfolk QOL-DN score in the period immediately following disease onset [32]. Furthermore, patients treated with placebo in other clinical studies in hATTR amyloidosis with polyneuropathy have shown worsening in QOL measures (Norfolk QOL-DN, SF-36) and neurologic impairment over 18–24 months [13,34,35].

A limitation of this study is that QOL burden may also extend to other domains not assessed in APOLLO, such that the full impact of hATTR amyloidosis on QOL may not be completely captured.

In conclusion, the APOLLO trial incorporated a range of different QOL measures, that were critical to fully assess the effect of patisiran on the multisystem nature of hATTR amyloidosis. Patisiran provided a significant and sustained improvement in QOL compared with placebo, with effects observed as early as 9 months. These data corroborate previous evidence of the significant benefit of patisiran on the disease manifestations that underpin QOL impairment in patients with hATTR amyloidosis with polyneuropathy [14]. The poor QOL observed in patients with this disease at baseline and the subsequent rapid deterioration without intervention, particularly seen at the earliest stages of disease, demonstrate the importance and benefit of diagnosing the disease as early as possible as well as initiating treatment early in the disease course.

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