Indirect Treatment Comparison of the Efficacy of Patisiran and Inotersen for hATTR Amyloidosis with Polyneuropathy

Laura Obici[1], Peter Gorevic[2], Hollis Lin[3], Jaclyn Franklin[3], Jihong Chen[3], Tim Lin[3], Gautam Sajeev[4], Jessie CH Wang[4], and Thomas H Brannagan[5]

[1]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Mount Sinai Medical Center, New York City, USA; [3]Alnylam Pharmaceuticals, Cambridge, USA; [4]Analysis Group, Inc., Boston, USA; [5]Department of Neurology, Columbia University, New York City, USA

Introduction

Background and Rationale

- Rare, rapidly debilitating, and fatal disease caused by a mutation in the transthyretin (*TTR*) gene that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and subsequent dysfunction across these multiple organs[1–5]
- Two therapies, patisiran (0.3 mg/kg IV q3w) and inotersen (284 mg SC qW), have demonstrated efficacy in pivotal, randomized, placebo-controlled, Phase 3 trials in patients with hATTR amyloidosis with polyneuropathy (APOLLO and NEURO-TTR, respectively)[6,7]
- APOLLO and NEURO-TTR had comparable inclusion/exclusion criteria and assessed a similar set of endpoints[6,7]
- In the absence of head-to-head randomized trials, indirect treatment comparisons (ITCs) can inform healthcare decision-making for patients with hATTR amyloidosis with polyneuropathy

Objective

- To indirectly compare the efficacy of patisiran and inotersen in hATTR amyloidosis with polyneuropathy

Methods

- A systematic literature scan identified data from randomized controlled trials on the efficacy of inotersen in hATTR amyloidosis with polyneuropathy; individual patient data for patisiran and placebo arms were taken from the APOLLO trial
- ITCs were conducted across important measures of polyneuropathy: mNIS+7$_{Ionis}$ (derived for APOLLO patients using components of NIS endpoints), Norfolk QOL-DN, PND score, and BMI
  - Comparisons could only be made on endpoints that were publicly available from the NEURO-TTR trial, such as the mNIS+7$_{Ionis}$
  - BMI was included instead of mBMI because interpretation of mBMI results for NEURO-TTR were confounded by observed changes in albumin levels that differed slightly between groups[8]
  - PND score was grouped by improvement or no change vs worsening; improvement and no change were grouped together since they are both positive treatment outcomes in this disease
- Timing of efficacy assessments:
  - To address the differential trial durations (18 month APOLLO vs 15 month NEURO-TTR), interpolated 15 month APOLLO outcomes were compared with reported 15 month outcomes in NEURO-TTR, where possible
- Degree and pattern of missing outcome data:
  - In NEURO-TTR, 22% of inotersen patients and 13% of placebo patients discontinued the study; corresponding numbers in APOLLO were 7% (patisiran) and 38% (placebo)
  - To assess the impact of differential rates of missingness between trial arms on estimated treatment effects, ITCs were conducted using outcome data based on pattern-mixture model (jump-to-reference [J2R] imputation) and mixed-effects model repeated measures (MMRM) (based on observed data)
  - Pattern-mixture model (J2R imputation):
    - Routinely requested by regulators when the degree and/or pattern of missingness could influence conclusions about treatment efficacy; reported in inotersen product monograph as measure of efficacy in a number of countries[9]
    - Assumes patients who discontinue from the trial have a mean response distribution equal to that of the placebo group
  - MMRM (based on observed data):
    - Prespecified analyses for both APOLLO and NEURO-TTR; based on missing at random assumptions without imputations for missing outcome values
- Distribution of baseline characteristics between trials:
  - Some minor differences in baseline characteristics are observed between APOLLO and NEURO-TTR studies
  - To account for these differences, both Bucher method and matching-adjusted indirect comparison (MAIC) analyses were conducted[10,11]

Results

- The systematic literature scan identified 26 reports for inotersen that refer to one Phase 3, randomized, placebo-controlled trial of inotersen in patients with hATTR amyloidosis with polyneuropathy (NEURO-TTR)
- Patisiran demonstrated a favorable treatment effect relative to inotersen across all analyses, with statistically significant differences observed for all pattern-mixture model (J2R imputation) analyses and the majority of MMRM (based on observed data) analyses (**Figures 1A–D**)
- After matching in the MAIC analysis, baseline distributions were balanced across the two trials for both treatment and placebo arms (**Table 1**)
  - The effective sample size for the matched APOLLO population was 137 patients (90 in the patisiran arm and 47 for the placebo arm)

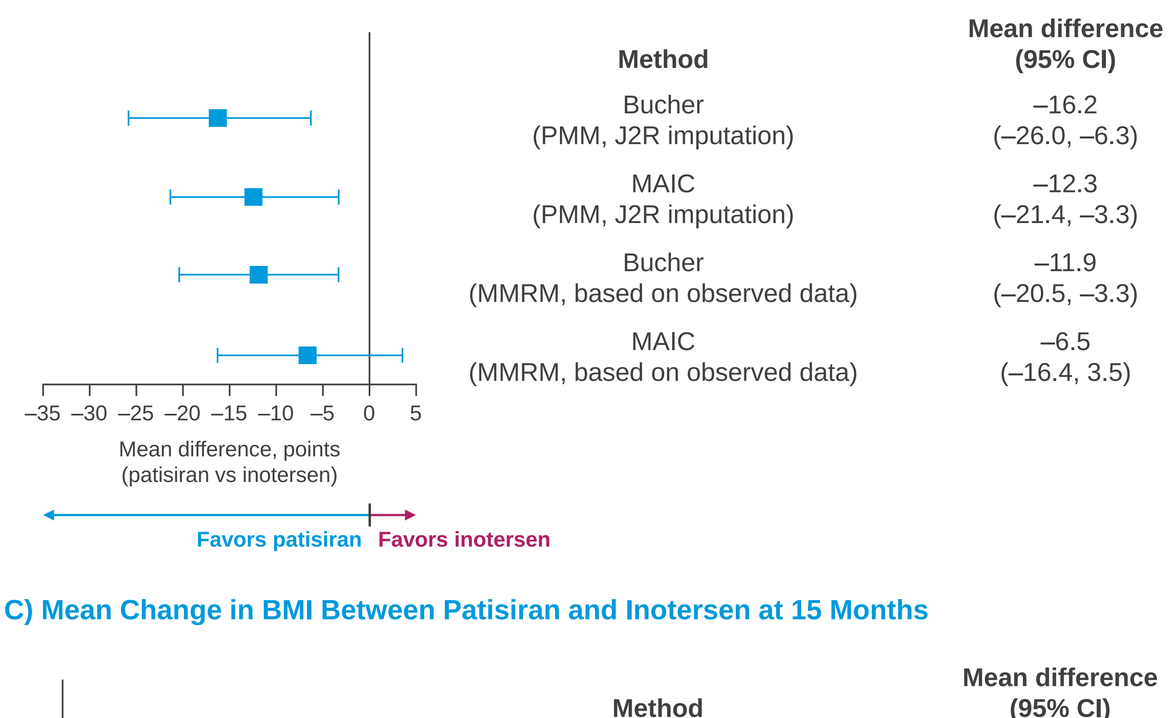
Table 1. Baseline Characteristics of APOLLO and NEURO-TTR after Matching

	NEURO-TTR		APOLLO	
	Inotersen	Placebo	Patisiran	Placebo
Age ± SD, years	59.0 ± 12.5	59.5 ± 14.0	59.0 ± 12.8	59.5 ± 11.3
Male, %	68.7	68.3	68.8	68.3
Race, %				
White	93.8	88.3	93.7	88.3
Non-white	6.3	11.7	6.2	11.7
BMI ± SD, kg/m^2	24.0 ± 4.9	24.2 ± 4.9	24.0 ± 4.3	24.2 ± 4.5
Previous stabilizer use, %	56.3	60.0	56.3	60.0
FAP stage, %				
FAP stage 1	66.1	70.0	66.1	70.0
FAP stages 2 and 3	33.9	30.0	33.9	30.0
V30M mutation, %	50.0	55.0	50.0	55.0
mNIS+7$_{Ionis}$ score ± SD	79.2 ± 37.0	74.8 ± 39.0	79.2 ± 44.0	74.8 ± 40.7
Norfolk QOL-DN score ± SD	48.2 ± 27.5	48.7 ± 26.7	48.2 ± 29.5	48.7 ± 24.5

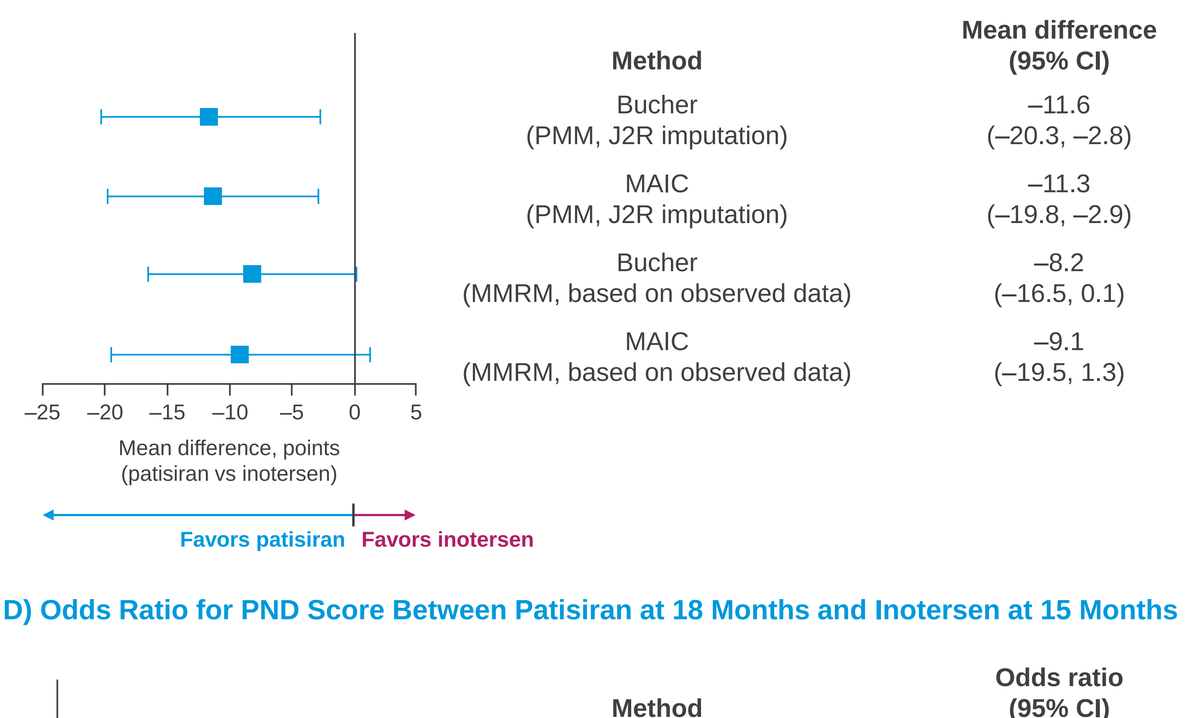
Differences in characteristics were not statistically significant following matching (p-value = 1.000 across all variables)

Figure 1. ITCs of the Efficacy of Patisiran and Inotersen

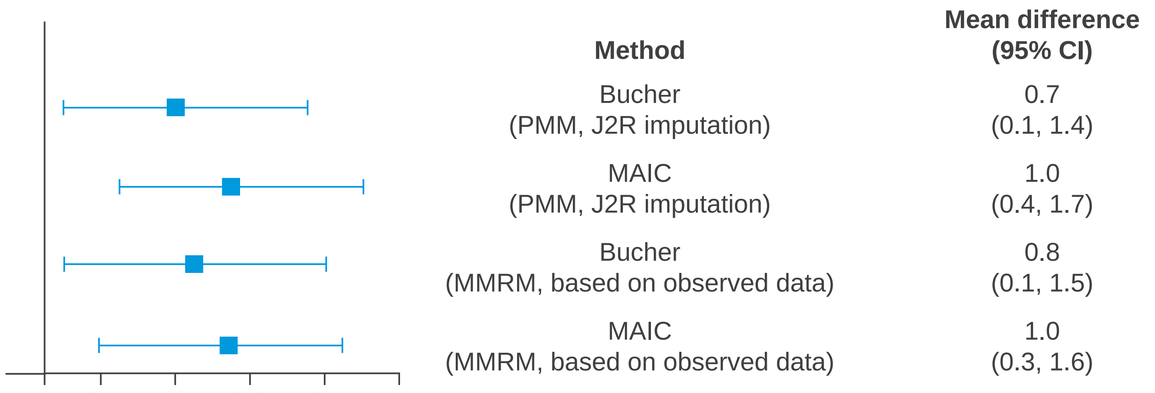
A) Mean Change in mNIS+7$_{Ionis}$ Between Patisiran and Inotersen at 15 Months



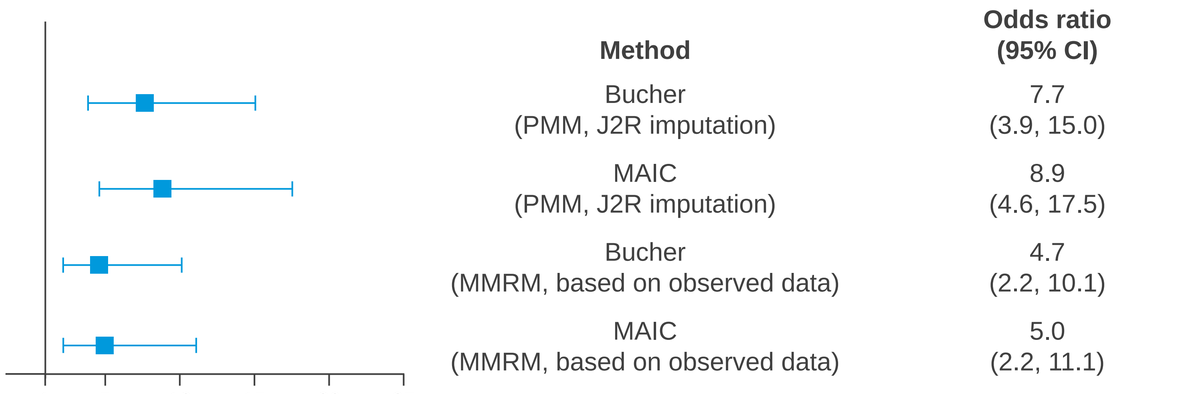
B) Mean Change in Norfolk QOL-DN Between Patisiran and Inotersen at 15 Months



C) Mean Change in BMI Between Patisiran and Inotersen at 15 Months



D) Odds Ratio for PND Score Between Patisiran at 18 Months and Inotersen at 15 Months



Limitations

- Comparisons from ITCs are limited to data that have been publicly reported
- MAICs cannot account for unmeasured factors in each trial

Conclusions

- In the absence of head-to-head randomized clinical trials, this analysis suggests patisiran had a favorable treatment effect on neuropathy and quality of life compared with inotersen in patients with hATTR amyloidosis with polyneuropathy; results were consistent across all analyses and approaches

APOLLO: patisiran = 148, placebo = 76 (1 patient in the placebo group in APOLLO was excluded from the ITC analyses due to missing baseline Norfolk QOL-DN measure); NEURO-TTR: inotersen = 112, placebo = 60

Abbreviations: BMI, body mass index; CI, confidence interval; FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated; ITC, indirect treatment comparison; IV, intravenous; J2R, jump-to-reference; MAIC, matching-adjusted indirect comparison; mBMI, modified body mass index; MMRM, mixed-effects model repeated measures; mNIS+7$_{Ionis}$, modified Neuropathy Impairment Score +7 used in IONIS trial; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PMM, pattern-mixture model; PND, polyneuropathy disability; q3w, every 3 weeks; qW, every week; QOL, quality of life; SC, subcutaneous; SD, standard deviation; TTR, transthyretin.

Acknowledgments: Editorial assistance in the development of the poster was provided by Adelphi Communications Ltd, UK, funded by Alnylam Pharmaceuticals.

Funding: This study was sponsored by Alnylam Pharmaceuticals.

References: 1. Adams et al. *Neurology* 2015;85:675–82; 2. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 3. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 4. Hawkins et al. *Ann Med* 2015;47:625–38; 5. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 6. Adams et al. *N Engl J Med* 2018;379:11–21; 7. Benson et al. *N Engl J Med* 2018;379:22–31; 8. European Medicines Agency. Tegsedi European Public Assessment Report 2018; 9. The Drug and Health Product Register. Tegsedi Product Monograph 2018; 10. Bucher et al. *J Clin Epidemiol* 1997;50:683–91; 11. Signorovitch et al. *Value Health* 2012;15:940–7.