Abstract: P560

Long-term treatment with inotersen and potential improvement of amyloid transthyretin cardiomyopathy

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Introduction: Amyloid transthyretin (TTR) amyloidosis cardiomyopathy (ATTR-CM) is a progressive and fatal disease caused by deposition of TTR in the heart. ATTR-CM may be caused by mutations in TTR (hereditary ATTR [hATTR]) or misfolding of normal TTR in older individuals (wild-type ATTR [wtATTR]). Natural history data show a progressive decline in cardiac functional and structural parameters including a reduction in 6-minute walk test (6MWT) distance and increase in left ventricular mass (LVM). Inotersen, an antisense oligonucleotide inhibitor of TTR production, showed efficacy in treating neuropathy in the NEURO-TTR study in patients with hATTR, including those with cardiac involvement. We previously reported stabilization of hATTR-CM and wtATTR-CM after 1 year of treatment with inotersen. We now report updated results for patients treated for up to 3 years.

Purpose: To study whether longer-term treatment with inotersen improves CM in patients with hATTR-CM and wtATTR-CM

Methods: Patients with biopsy proven hATTR-CM or wtATTR-CM, interventricular septum (IVS) thickness = 1.3 cm on echo, and evidence of congestive heart failure [CHF]) received 300 mg inotersen by subcutaneous injection weekly in a single-center, ongoing, open-label, investigator-initiated study. Safety monitoring included platelet counts, serum creatinine, and urine protein. Efficacy assessments included plasma TTR levels, 6MWT distance, B-type natriuretic peptide (BNP) and echocardiograms and cardiac MRIs.

Results: As of October 2018, 35 patients (10 hATTR, average age 63.4 years and 25 wtATTR, average age 76.1 years) have enrolled. Of the 35 patients, 5 are newly enrolled, 21 completed 1 year, 17 completed 2 years, 14 completed 3 years, 3 completed 4 years, 8 voluntarily withdrew, and 1 died from a nondrug related cause. Inotersen was well-tolerated. No drug-related serious adverse events (AEs), cases of severe thrombocytopenia, or renal AEs occurred. Sustained TTR reduction resulted in a mean decrease in LVM by 0.54%, 8.5%, and 11.4% and improvement in 6MWT of 5.6, 23.2, and 18.6 meters compared to baseline at 1, 2, and 3 years respectively in all patients. Improvement in 6MWT was more striking in the hATTR subgroup, who demonstrated a mean improvement of 29.3, 40.9, and 50.2 meters compared to baseline at 1, 2, and 3 years respectively. BNP and IVS thickness decreased or remained stable in most patients and left ventricular ejection fraction (LVEF) increased or remained stable in most patients.

Conclusions: Long-term treatment with inotersen was well-tolerated and resulted in improvement or stabilization in cardiac function and structure in patients with hATTR-CM and wtATTR-CM. Our findings showing that long term inotersen therapy resulted in an increase in 6MWT distances, stabilization of the LVEF and BNP, and decreased LVM suggest that inotersen has the potential to decrease amyloid burden, reverse amyloid cardiomyopathy, and improve quality of life and survival.