Effect of migalastat on cardiac involvement in Fabry disease: preliminary results from MAIORA study

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Background: Fabry Disease (FD) is a rare X-linked lysosomal storage disorder. Since 2016, pharmacological chaperone Migalastat has been approved for treatment of FD patients with amenable mutations to stabilize defective forms of the enzyme α-galactosidase A. A small but significant reduction in left ventricular (LV) mass after 18 months of Migalastat treatment has been previously reported by echocardiography. However, an integrated assessment of the effect of Migalastat on cardiac involvement, combining LV morphology and tissue composition by CMR with exercise capacity by cardiopulmonary test, is lacking.

Purpose: To determine the effects of 18 month treatment with Migalastat on LV mass, native T1 value and functional capacity in naïve patients with genetically confirmed FD cardiomyopathy.

Methods: Sixteen treatment naïve FD patients (4 females, mean age 46.4±16.2) with amenable mutations and signs of cardiac involvement underwent CMR with T1 mapping and cardio-pulmonary testing before and after 18 months of migalastat therapy as a part of MAIORA Study. Cardiac involvement was defined as presence of reduced native T1 values at CMR (a surrogate of myocardial glycosphingolipid storage) and/or LV hypertrophy (LVH). Nine patients (56%, 2 females, mean age 56.4±12.7 years) had LVH at baseline.

Results: Migalastat treatment was well tolerated in all patients, with no serious adverse event. No change in LV mass was detected at 18 months compared to baseline (95.2 (66.0–184.0) vs 103.0 (71.0–182.0) g/m^2; p=0.5516). The same result was found after stratifying patients according to presence/absence of Late Gadolinium Enhancement (LGE) (LGE+ n=8, 2 females, mean age 56.2±13.1 years). There was a trend towards an increased native septal T1 value (870.0 (848–882) vs 860.0 (833.0–875.0) ms at baseline; p 0.056) with unchanged extracellular volume (ECV) (0.26 (0.23–0.028) vs 0.26 (0.22–0.29) at baseline; p 0.276) in the overall cohort. An improvement in functional capacity with a trend towards an increase in percent-predicted peak VO2 (72.0 (61.25–80.75) vs 67.0 (45.2–79.2) at baseline; p 0.056) and a significant increase in VO2 at anaerobic threshold (14.8 (12.6–20.0) vs 13.10 (6.8–18.6) ml/kg/min at baseline; p 0.004) was reported in the total population.

Conclusion: In treatment naïve FD patients with amenable mutations and signs of early or overt cardiac involvement, 18-month treatment with Migalastat stabilized LV mass both in patients with and without LGE and was associated with an improvement in exercise tolerance. The trend towards an increase in T1 value associated with unchanged ECV suggests partial clearance of cardiomyocyte glycoshingolipid storage. These real-world data are consistent with a beneficial impact of migalastat on the progression of cardiac involvement in FD.

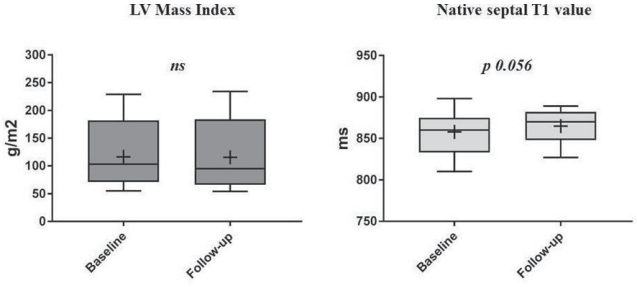

Fig.1: Box plot representing median, lower and upper quartile for LV mass index (g/m2) and native septal T1 value (ms) at baseline and follow up
LV left ventricle