Podocyte globotriaosylceramide (GL-3) content in female adult patients with Fabry disease and amenable mutations reduces following 6 months of treatment with migalastat

Behzad Najafian, Forough Sargolzaeiaval, Alexey Sokolovskiy and Michael Mauer
Podocyte globotriaosylceramide (GL-3) content in female adult patients with Fabry disease and amenable mutations reduces following 6 months of treatment with migalastat

Behzad Najafian, Forough Sargolzaei, Alexey Sokolovskiy, Michael Mauer, University of Washington, Seattle, WA, United States, University of Minnesota, Minneapolis, MN, United States

GL-3 accumulation is associated with podocyte injury and loss in Fabry disease (FD). Reducing intracellular GL-3 is an important goal of FD treatment. Migalastat 150 mg QOD (MIG) reduces peritubular capillary GL-3 in FD patients. While GL-3 reduction in podocytes following 6 months of migalastat treatment had been documented in males, assessment of this effect in females has been complicated by mosaicism. Using a novel unbiased approach, we examined if MIG can reduce total volume of GL-3 inclusions [V(Inc/PC)] in FD affected podocytes independent of mosaicism. Paired kidney biopsies from 17 ERT naïve females with FD at baseline and after 6 months MIG treatment were studied by masked unbiased electron microscopy stereology. All patients had GLA mutations amenable to MIG with a median age of 44 years (27–68). The average V(Inc/PC) was decreased from a mean of 2578 ± 1167 at baseline to 1746 ± 779 μm³ after 6 months MIG (p = .015). This decrease correlated with decreased mean podocyte volume [4512 ± 1915 μm³ at baseline, 3147 ± 1523 μm³ after 6 months MIG (r = 0.93, p < .0001)], indicative of podocyte cytoplasmic shrinkage proportional to GL-3 loss. Thus, the volume fraction of podocyte cytoplasm filled with GL-3 did not change significantly. Importantly, podocyte GL-3 volume at baseline was directly related to the extent of GL-3 loss within 6 months (r = −0.80, p < .0001). There was a trend for decline in plasma lyso-GL3 from baseline (15 ± 7 nM) after 6 months MIG (13 ± 7 nM; p = .079), but this was not correlated with the reduction in V(Inc/PC). No significant change in albuminuria, proteinuria or GFR was observed after 6 months of MIG. Our studies suggest that podocytes in females with FD and amenable mutations benefit from MIG by losing their GL-3 inclusions. (Supported by an investigator initiated grant from Amicus.)
