Six months of Migalastat Treatment Reduces Podocyte Globotriaosylceramide Content in Adult Male Patients with Fabry Disease

Najafian B. 1, Sokolovskiy A. 1, Barth J. 2, Castelli J. 2, Williams H. 2, Mauer M. 3


Background

- Deficiency of α-galactosidase-A in Fabry disease leads to accumulation of globotriaosylceramide (GL3) inclusions in cells, causing organ damage. Progressive kidney failure is a major complication of Fabry disease.
- Podocytes are terminally differentiated cells with limited regeneration capacity. Recent studies suggest a key role for podocytes in Fabry nephropathy. In young Fabry patients, we showed that podocyte GL3 accumulation occurs early, is progressive with age, and is associated with podocyte injury and proteinuria (Najafian et al. Kidney Int 2011). Reducing podocyte GL3 burden may reduce progression of Fabry nephropathy. However, podocytes are far more resistant than other kidney cells to clear GL3 following enzyme replacement therapy.
- Migalastat (MIG) is an investigational pharmacological chaperone that stabilizes “amenable” mutant α-gal-A and enhances its trafficking to lysosomes. MIG reduced peritubular capillary endothelial cell GL3 in 6 months (study 011).

Hypothesis

MIG reduces GL3 inclusion content in podocytes in patients with Fabry disease with amenable mutations.

Materials and Methods

- 8 paired biopsies (baseline and 6 months post-migalastat) from male patients with “amenable” GLA mutations

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* Asterisk indicates patients with no paired biopsies after 6 months migalastat (e.g. only BL and 06 on placebo)

Data includes all amenable male patients with CF and paired assessable biopsies

Biopsy structural parameters by electron microscopic stereology

- Vv(Inc/PC): Fraction of podocyte cytoplasm occupied by GL3 inclusions
- VPC: Average podocyte volume
- V(Inc/PC): Average volume of GL3 inclusions per podocyte

Other Parameters

- Age, eGFR, 24 hr urine protein, albumin/creatinine ratio, protein/creatinine ratio, plasma lyso Gb3, and peritubular capillary inclusion score (BLISS)

Results

Figure 1. (A) Volume of GL3 inclusions per podocyte was reduced from baseline (BL) to 6 months (6M) post-treatment. (B) A glomerulus from a Fabry patient at baseline; and (C) 6 months after migalastat.

Figure 2. (A and B) GL3 reduction in podocytes was closely paralleled by a reduction in podocyte size. Likewise, the magnitude of foot process width reduction correlated with the magnitude of reduction in GL3 inclusion volume in podocytes. Likewise, the magnitude of foot process width reduction correlated with the magnitude of reduction in GL3 inclusion volume density in podocytes (R=0.82, p=0.02) and reduction in podocyte size (R=0.089, p=0.007).

Figure 3. (A) Average foot process width in Fabry patients before or after 6 months treatment with migalastat was greater than values from 9 healthy control subjects. Foot process width was reduced in 5/7 and increased in 2/7 cases after 6 months MIG, but the change was not statistically significant. (B) The decrease in foot process width was correlated with the reduction in GL3 inclusion volume in podocytes. Likewise, the magnitude of foot process width reduction correlated with the magnitude of reduction in GL3 inclusion volume density in podocytes.

Figure 4. (A) Plasma lyso Gb3 was reduced after 6 months treatment. (B and C) The decrease in plasma lyso-Gb3 correlated with %change in GL3 inclusion content of podocytes from baseline to 6 months.

Figure 5. (A and B) There were statistical trends towards associations between 24-hr urine protein and % change in GL3 inclusion content of podocytes.

Conclusions

- In patients with Fabry disease and “amenable” mutations, migalastat treatment led to a reduction in podocyte GL3 within 6 months. This reduction correlated with proportional reduction in podocyte volume, leading to no significant change in GL3 volume fraction in podocytes.
- The observed direct relationship between reduction in foot process width and GL3 content in podocytes following 6 months of migalastat treatment is suggestive of reduced podocyte injury.
- It will be crucial to confirm these findings in larger cohorts and examine if with longer treatment duration, podocytes further benefit from migalastat treatment.
- Future studies are needed to confirm if migalastat can prevent or ameliorate podocyte loss.
- This study shows that sensitive quantitative stereological methods can assess treatment efficacy in much shorter time periods (e.g. 6 months) than scoring methods.

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