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

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Background

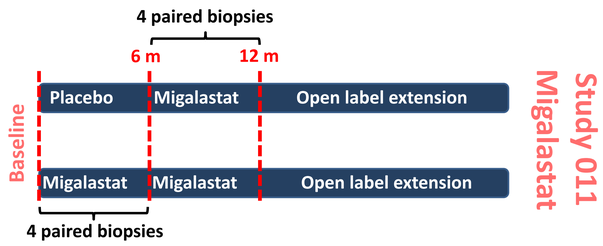
- Deficiency of α-galactosidase-A in Fabry disease leads to accumulation of globotriaosylceramide (GL-3) inclusions in cells, causing organ damage. Progressive kidney failure is a major complication of Fabry disease.
- Podocytes are terminally differentiated cells with limited regeneration capacity. Recent studies suggest a key role for podocytes in Fabry nephropathy. In young Fabry patients, we showed that podocyte GL-3 accumulation occurs early, is progressive with age, and is associated with podocyte injury and proteinuria (Najafian et al. Kidney Int 2011). Reducing podocyte GL-3 burden may reduce progression of Fabry nephropathy. However, podocyte are far more resistant than other kidney cells to clear GL-3 following enzyme replacement therapy.
- Migalastat (MIG) is an investigational pharmacologocal chaperone that stabilizes "amenable" mutant α-gal-A and enhances its trafficking to lysosome. MIG reduced peritubular capillary endothelial cell GL-3 in 6 months (study 011).

Hypothesis

MIG reduces GL-3 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



No	Sex	Age	GLA Mutation	eGFR	UPr-24 (mg)	ACR (g/g)
1	M	25	D55V/Q57L	114	198	6
2*	M	33	D244N	115	349	14
3	M	34	Y216C	119	400	16
4	M	35	G144V	105	240	1
5	M	45	L243F	102	161	2
6	M	45	P259R	105	335	7
7*	M	45	P259R	86	1909	119
8	M	45	A156T	74	247	4
9	M	52	D33G	82	367	9
10*	M	56	R301Q	56	2351	126
11	M	60	D322E	41	918	34

* Asterisk indicates patients with no paired biopsies after 6 months migalastat (e.g. only BL and M6 on placebo)
**Data includes all amenable male patients with ICF and paired assessable biopsies

Biopsy structural parameters by electron microscopic stereology

- Vv(Inc/PC): Fraction of podocyte cytoplasm occupied by GL-3 inclusions
- V(PC): Average podocyte volume
- V(Inc/PC): Average volume of GL-3 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

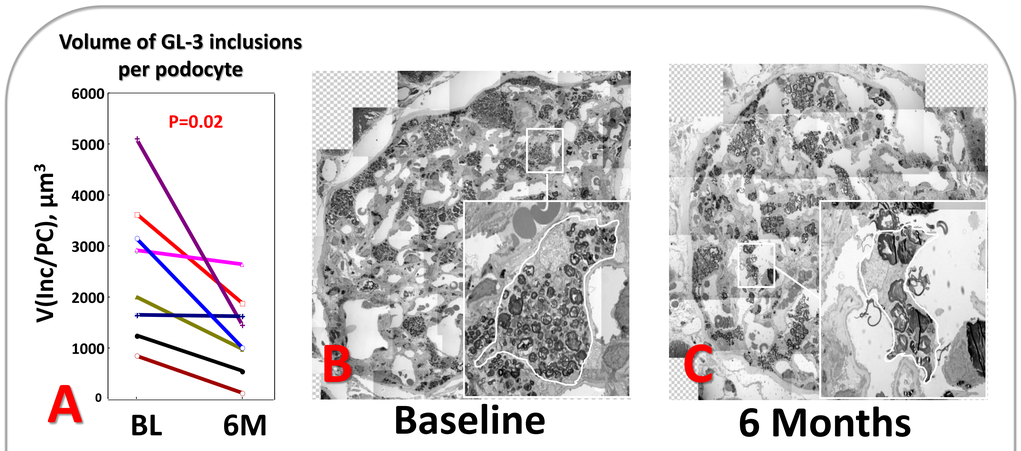


Figure 1. (A) Volume of GL-3 inclusions per podocyte was reduced from baseline (BL) to 6 months (6M) post-treatment. (B) A glomerulus from a Fabry patient at baseline; and (C) 6 months after migalastat.

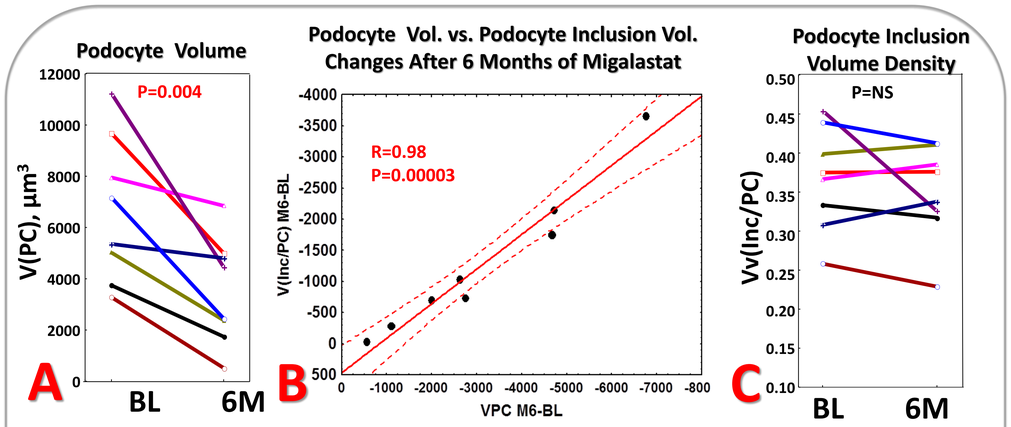


Figure 2. (A and B) GL-3 reduction in podocytes was closely paralleled by a reduction in podocyte volume. (C) Volume fraction of GL-3 inclusions in podocytes did not change during the 6 months migalastat treatment.

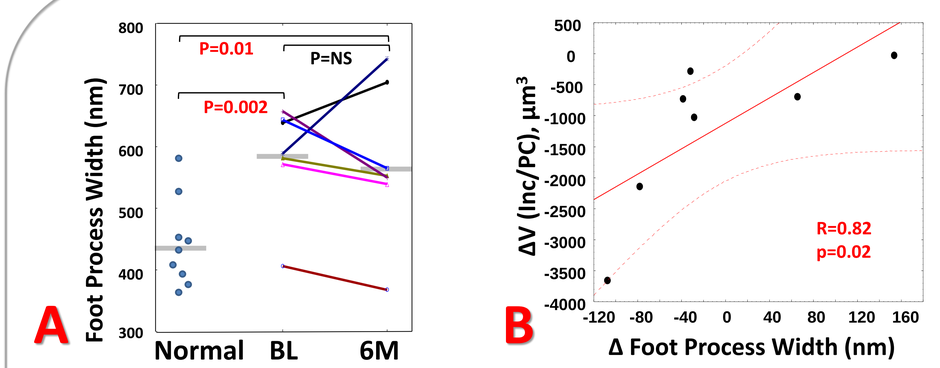


Figure 3. (A) Average foot process width in Fabry patients before or after 6 months treatment with migalastat was greater than values from 9 healthy control subjects . Foot process width was reduced in 5/7 and increased in 2/7 cases after 6 months MIG, but the change was not statistically significant. (B) The magnitude of foot process width reduction correlated with the magnitude of reduction in GL-3 inclusion volume in podocytes. Likewise, the magnitude of foot process width reduction correlated with the magnitude of reduction in GL-3 inclusion volume density in podocytes (R=0.82, p=0.02) and reduction in podocyte size (R=0.089, p=0.007).

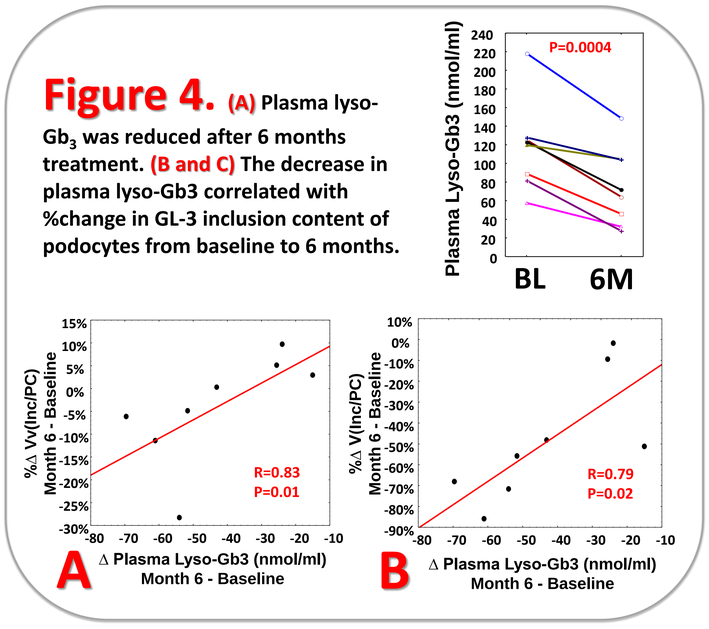


Figure 4. (A) Plasma lyso-Gb_3 was reduced after 6 months treatment. (B and C) The decrease in plasma lyso-Gb3 correlated with %change in GL-3 inclusion content of podocytes from baseline to 6 months.

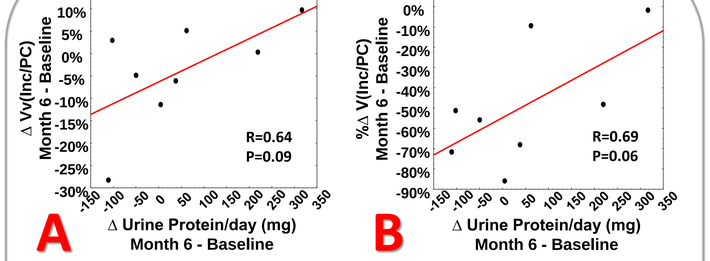


Figure 5. (A and B) There were statistical trends towards associations between 24-hr urine protein and % change in GL-3 inclusion content of podocytes.

No statistically significant changes in eGFR, albuminuria or proteinuria over 6 months treatment.

Conclusions

- In patients with Fabry disease and "amenable" mutations, migalastat treatment led to a reduction in podocyte GL-3 within 6 months. This reduction correlated with proportional reduction in podocyte volume, leading to no significant change in GL-3 volume fraction in podocytes.
- The observed direct relationship between reduction in foot process width and GL-3 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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