# Nine-year follow-up in a patient receiving migalastat pharmacological chaperone therapy for Fabry disease

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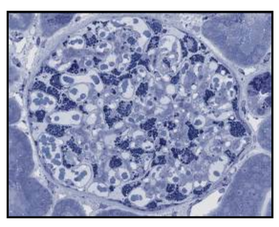
## BACKGROUND

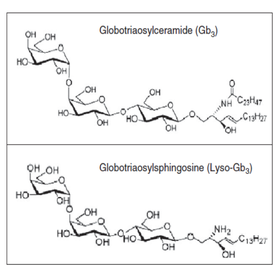
**Fabry Disease**

Fabry disease is a rare, progressive, and devastating X-linked lysosomal storage disorder caused by a deficiency in α-galactosidase A, with an estimated prevalence of 1:117,000 to 1:40,000 (Desnick and Schindler 2001; Meikle et al. 1999; Eurordis 2005).



More than 800 disease-causing mutations in *GLA* have been identified; ~60% of these are missense mutations.

Affects males and females; females have a mosaic of healthy and diseased cells.




*From Auray-Blais et al., 2010*

The cardinal presenting features of Fabry disease are intermittent acroparesthesia and episodic crises of pain and fever (especially in childhood), angiokeratomas, hypohidrosis, heat/cold intolerance, and a characteristic "whorled" corneal opacity that generally does not affect vision. In these patients, the major causes of mortality include renal failure, cardiomyopathy, and cerebrovascular accidents.

Globotriaosylceramide (GL-3), a natural substrate of α-Gal A, accumulates and affects multiple organs and organ systems (kidney, heart, brain, gastrointestinal, skin).

Globotriaosylsphingosine (lyso-Gb3) is another substrate of α-Gal A that is elevated in plasma of males and females living with Fabry disease.

## FABRY PAIN: OVERVIEW

The neurological manifestations of Fabry disease include both peripheral and central nervous system involvement caused by a deficiency of α-Gal A and accumulation of a–D-galactosyl moieties, particularly GL-3. These are found in Schwann cells and dorsal root ganglia together with deposits in central nervous system neurons (Schiffman, 2006).

Involvement of the peripheral nervous system affects mainly small Aδ and C fibers and is likely causally related to the altered autonomic function and neuropathic pain found in this disorder (Schiffman, 2006).

Characteristics

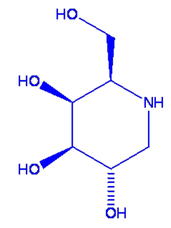
- Onset in the first 20 years
- Burning, deep ache, shooting pain
- Continuous or episodic pain
- Heat-, exercise-, infection-, stress-induced pain
- Poor heat tolerance
- Poor cold tolerance
- Hypohidrosis
- Eventual decreases cold and heat perception (increased threshold)

Treatment

- The pain associated with Fabry disease can be managed with analgesics, but non-steroidal anti-inflammatory drugs are generally ineffective and narcotic analgesics should be avoided where possible because of potential dependency problems.
- Phenytoin, carbamazepine, gabapentin, tricyclic antidepressants and topiramate have all been used to manage pain in Fabry disease.

## MIGALASTAT FOR FABRY DISEASE

Migalastat is an orally administered investigational pharmacological chaperone for patients with amenable mutations; facilitates proper folding and cellular trafficking of amenable mutant forms of α-Gal A to lysosomes where the breakdown of substrate can proceed.




Migalastat
Deoxygalactonojirimycin
AT1001

Amenable mutant forms of α-Gal A are identified using a GLP-validated HEK-293 cell-based assay (GLP HEK assay; see below).

30-50% of patients with Fabry disease are estimated to have amenable mutations; the majority of amenable mutations are associated with the classic phenotype of the disease.

## DEFINITION OF AMENABILITY

The GLP HEK assay was used to express each of 600 FD-causing mutations in HEK-293 cells and measure increases in α-Gal A activity in response to migalastat. Amenable mutant forms were defined by a relative increase of ≥1.2-fold and absolute increase of ≥3% wild-type in the presence of 10 μM migalastat.

## OBJECTIVE AND METHODS

We describe the long-term effects of migalastat on FD-associated pain.

A 37-year-old male patient with Fabry disease presenting with severe acroparesthesia and sensation of stiffness predominantly in the lower extremities, was evaluated. Clinical and biochemical studies were performed. Use of concomitant pain medications was also monitored.

## CASE REPORT

A 37-year-old male patient presented in 2005 with an 8-year history of severe acroparesthesia in hands and feet and sensation of stiffness predominantly in the lower extremities that markedly affected his quality of life.

As a young student, he began to feel occasional burning in his feet (arches, heels and Achilles). However, in his late 20's, the pain worsened and became chronic, making him very fatigued. He would awake with extreme soreness and stiffness with both continuing during the day. He was treated with multiple pain medications including daily oxycodone, tizanidine and baclofen and over-the-counter analgesics (such as acetaminophen, naproxen, ibuprofen).

On neurologic examination at age 37 years, the patient had mild decrease in light touch, pinprick, temperature in right ulnar aspect of upper extremity and both feet up to ankles, and decrease vibration in left lateral foot. Sensation of stiffness predominantly in the lower extremities and headaches since 2000. He had no cutaneous (angiokeratomas) or ocular manifestations (corneal opacities) of Fabry disease. No findings on echocardiography or cardiac MRI.

The patient was diagnosed with Fabry disease in 2005 following a kidney biopsy showing typical lysosomal inclusions in podocytes. The patient's WBC α-Gal A was markedly decreased 5.4 nmol/hour/mg protein (13.4% - 25% of normal) resulting from an A143T mutation.

Shortly after diagnosis, the patient began (in January 2006) receiving migalastat (various doses) for 4.5 years of treatment (phase 2 trial). This was followed by 150 mg every other day for an additional 4.5 years (phase 2 and 3 open-label extension trial), with no drug-related adverse events observed.

## RESULTS: CONCOMITANT PAIN MEDICATION

**Phase 2**

First 4.5 years migalastat treatment

During the first phase 2 trial (dose finding), α-Gal activity increased 5-fold in leukocytes and 30-fold in skin after 72 weeks of migalastat treatment. Cardiac and renal function, as well as urine GL-3 levels remained normal.

**Phase 3 (open label extension)**

**Y**ears 4.5 to 9

During the phase 3 migalastat treatment (150 mg QOD), paresthesias and sensation of stiffness progressively improved, and he was able to decrease and then discontinue all his pain medications by the 8th year of therapy.

4.5 years → 4.5 years still ongoing

| Phase 2 studies various migalastat doses | Phase 3 study migalastat 150 mg QOD |
|---|---|
| Pain meds: Dose XX (TID*)<br>1. oxycodone, tizanidine, baclofen<br>2. acetaminophen, naproxen, ibuprofen | Change in pain meds<br>Dose XX TIB → Dose Y BID → Dose Z Once daily → January 2015: STOP (oxycodone, tizanidine, baclofen, acetaminophen) PRN (ibuprofen, naproxen) |

*Abbreviations: TID (three times a day); BID (two times a day); PRN (as needed)*

Pain medications (use):

- oxycodone, tizanidine, baclofen, acetaminophen (stopped)
- naproxen, ibuprofen (as needed)

As of January 2015 he is no longer taking the relaxants and opiates. He feels well, goes to the gym three times a week to lift weights and works, where he is either walking extensively every day or digging holes and bending down frequently in the heat of summer. None of this was possible for him before migalastat therapy.

## CONCLUSIONS

Migalastat, administered for a duration of 9 years in a single patient with Fabry disease was associated with:

- An increase in α-Gal A activity in leukocytes and in skin following 1.4 years treatment with migalastat with normal cardiac and renal functions.
- Progressive improvement in paresthesia and sensation of stiffness was noted between years 4.5 and 9 of treatment with migalastat resulting in no reliance on daily pain medications in year 8 of treatment.

## REFERENCES

1. Schiffman, 2006.
2. Desnick and Schindler, 2001.
3. Meikle et al. 1999.
4. Eurordis, 2005.