Pharmacologic Chaperone Responsiveness in Canadian Patients with Fabry Disease

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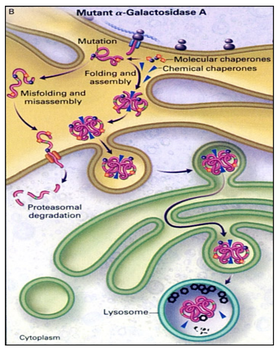
Introduction

- Fabry disease is a common lysosomal storage disease in Canada
- Caused by deficiency of α-galactosidase enzyme
- GLA gene mutation on X chromosome
- Results in premature death from renal failure, strokes and hypertrophic cardiomyopathy
- Treatment consists of cardiovascular risk factor reduction and enzyme replacement therapy (ERT), which is given every 2 weeks intravenously.
- ERT reduces the rate of decline in GFR and the rate of increase in left ventricular wall thickness
- ERT is not a cure and costs Canadian taxpayers $300,000 per year/patient for a total of about $61.5M annually.

Chaperone Therapy

- Pharmacologic chaperone therapy with Migalastat, an oral iminosugar, increases residual enzyme activity by stabilizing the molecule and delivering more enzyme to the lysosome.
- Studies suggest this may decrease cardiac wall thickness and stabilize renal function. (Germain *et al* NEJM 2016;375:545.)
- We report the results of a survey of Fabry disease patients in Canada to determine the prevalence of chaperone responsiveness as a guide to planning future therapy.



Frustaci *et al* NEJM 2001; 345:25-32

Methods

- The Canadian Fabry Disease Initiative (CFDI) is a registry of 466 Fabry disease patients followed for up to 10 years. All known GLA mutations in CFDI patients were evaluated using a published library of chaperone-responsive mutations based on an in vitro HEK cell assay. (Benjamin *et al* Genetics in Medicine 2017;19:430, supplemental tables S11A,B).
- Of 814 mutations 241 (29.6%) were large mutations (deletions, duplications, truncations, frame shift and splice site) and categorized as non-responsive mutations without testing.
- Of the smaller mutations (missense mainly), 268 were chaperone responsive (32.9%) and 332 (40.8%) were not.

Results

- The majority of Canadian Fabry disease patients are enrolled in the CFDI with ascertainment of 92%; over 95% have been genotyped.
- We evaluated 404 Fabry disease patients in the CFDI study who had genotyping done: 143 males, 261 females, mean age 45.0±17.8 (sd), range 8-86 years.
- Prevalence of ERT use under current Canadian Fabry Treatment Guidelines was 50.0%.

Canadian ERT Treatment Guidelines 2016

- Kidney disease - low GFR, NDI, Fanconi syndrome, hypertension, proteinuria
- Heart disease - incr WT, LVH, LVMI, arrhythmia, heart block, diastolic CHF, incr LA, VHD, abn tissue doppler, cMRI LE
- TIA/strokes, acute hearing loss confirmed by a neurologist
- Uncontrolled GI symptoms
- Uncontrolled neuropathic pain

www.garrod.ca./wp-content/uploads/Canadian-FD-Treatment-Guidelines-2016.pdf

Response to Chaperone Therapy

- Chaperone responsiveness in 23 mutations was noted in 86 patients (21.3%), of whom half were receiving ERT (Table 1).
- Non-responsive mutations (n=67) were found in 318 patients (78.7%) (Table 2).
- Most patients with chaperone responsive mutations had classic Fabry disease phenotype (72.1%), rather than variant (24.4%) or indeterminate (3.5%) phenotypes.

Table 1 Chaperone Responsive Mutations

p.Leu54Pro	p.Leu243Phe
p.Arg112His	p.Pro259Leu
p.Ala143Thr	p.Pro293Thr
p.Ala156Thr	c.937G>T
p.Phe169Ser	p.Ile317Thr
p.Met187Val fs*6	p.Ile319Thr
p.Leu191Gln	p.Gln321Leu
p.Pro205Thr	p.Gin321Arg
p.Pro214Leu	p.Ser345Pro
p.Asp215Ser	p.Arg356Trp
c.695T>C	p.Gly361Ala
	p.Arg363Cys

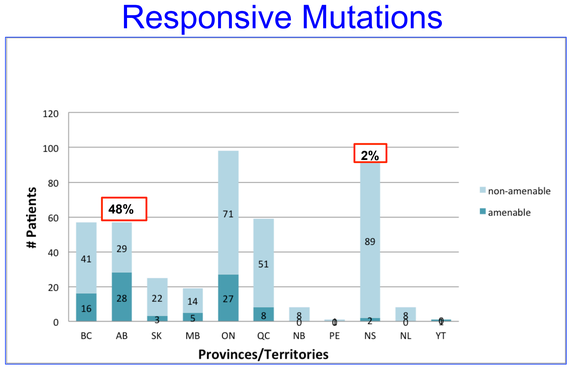
Table 2 Chaperone Non-Responsive Mutations

p.Met1Thr
g.35del13
c.101dupA (p.Asn34Lys fs*22)
c.128G>T (p.Gly43Val)
c.136C->T (p.His46Tyr)
c.139T>G (p.Trp47Gly)
c.194+1562_370-892del
c.195-?547+?del
c.233->G (p.Ser78X)
c.234delA (p.Glu79Lys fs*42)
p.Trp81Ser
c.242G>A (p.Trp81X)
c.253G>A (p.Gly85Met)
c.266T->C (p.Leu89Pro)
c.299G>C (p.Arg100Thr)
c.317_327del (p.Leu106 fs)
c.335G>A (p.Arg112His)
c.325C>T (p.Arg118Cys)
intron2:c.369+5G>T
c.370-533_c.1277del4.5kb
p.His125Pro/+
c.401A>C (p.Try134Ser)
c.422C>T (p.Thr141Ile)
p.Ala143Pro
p.His125Pro/+
c.401A>C (p.Try134Ser)
c.422C>T (p.Thr141Ile)
p.Ala143Pro
c.612G>A (p.Trp204X)
c.618_621delinsAAA (p.Tyr207Lys fs*33)
c.639+919G>A (IVS4+914 G>A)
p.Arg220X
c.680G>A (p.Arg227Gln)
c.679C>T (p.Arg227X)
p.Trp236Leu
p.Val254Gly fsX10
c.761_763delTTG
c.774_775delAC (p.Gly258 fs)
c.774_del (p.Pro259Arg fs)
c.782G>T (p.Gly261Val)
c 802-3_804delin
p.Asn272Ser
g.8320 g>a
c.854C->A (p.Ala285Asp)
p.Pro293Thr
c.878C>T (p.Pro293Leu)
p.Gln321Glu
c.961C>G (p.Gln321Glu)
c.893insG
c.1000-2 A>G [r.(spl?)]
c.1012G>A (p.Glu338Lys)
p.Arg342X
p.Arg342Gln
c.1025G>A (p.Arg342Gln)
g.9073del3 (seqX14448)
g.9363insA
c.1033_1034del (p.Ser345fs)
p.Ala348Pro
p.Try349X
c.1049delC (p.Ala350fs)
c.1066C>T (p.Arg356Trp)
c.115T>G (p.Leu372Arg)
c.1121_1123 del (p.Lys374_Gly375del)
c.1156C>T (p.Gln386X)
c.1201dupT
g.14016A>C (NG_007119.1)
p.Ala401Cys
p.Leu414Ser

Distribution

- There was an uneven geographic distribution of chaperone responsive mutations. (Figure 1)
- Alberta had 25 patients (prevalence 48.1%) compared with Nova Scotia with only 2 patients (2.2%).
- This is due to the presence of a founder effect in Nova Scotia with a large kindred with an A143P mutation that was chaperone non-responsive.

Figure 1 Distribution of Chaperone Responsive Mutations



Discussion

- Chaperone therapy for Fabry disease has several advantages over the current gold standard of ERT:
  - Oral, every second day
  - No infusion reactions or iv access
- Manufacturer (Amicus) has application pending with Health Canada, with a decision anticipated Q4 2017 or Q1 2018.
- Cost uncertain but may equal ERT at $300,000/year/patient.

Conclusions

- Oral chaperone therapy for Fabry disease could potentially be used in about one fifth of the current Canadian FD population.
- Only half of those patients meet the current Canadian Fabry disease treatment guidelines for ERT suggesting that chaperone therapy would only be possible in up to 40 (10%) of Fabry disease patients in Canada.
- Whether use of chaperone therapy would have any clinical or cost advantage over ERT is unknown.

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