

infantile-onset Pompe disease (IOPD) who had previously received alglucosidase alfa for ≥ 6 months and demonstrated either clinical decline or sub-optimal response. In the 25-week primary analysis phase, participants ($n = 22$) received avalglucosidase alfa 20 or 40 mg/kg IV every other week (qow) or their pre-enrollment stable dose of alglucosidase alfa (range: 20 mg/kg qow to 40 mg/kg weekly). In a previous presentation of preliminary efficacy data (WORLDSymposium™ 2020), overall positive trends (stabilization or improvement) in Gross Motor Function Measure-88 (GMFM-88), Pompe-Pediatric Evaluation of Disability Inventory (PEDI) Functional Skills Scale: Mobility Domain, and echocardiographic left ventricular mass (LVM) Z-score were demonstrated with avalglucosidase alfa. Levels of the pharmacodynamic disease biomarkers for muscle damage (creatinine kinase) and glycogen burden (hexose tetrasaccharide) also decreased with avalglucosidase alfa compared to stability with alglucosidase alfa. To further characterize treatment responses, analyses of individual patient-level results, eyelid measurements to evaluate for extent of ptosis, and immunogenicity have been conducted. The patient-level analyses confirm that avalglucosidase alfa at 20 and 40 mg/kg qow appears to improve or better stabilize symptoms compared with alglucosidase alfa (20 mg/kg qow to 40 mg/kg weekly) with regard to pharmacodynamic disease biomarkers, motor outcomes, cardiac parameters, and eyelid measures. The highest dose of avalglucosidase alfa tested, 40 mg/kg qow, appears to afford additional benefits in meaningful outcome measures, while maintaining a favorable safety profile and acceptable immunogenicity. There were no serious or severe treatment-related treatment-emergent adverse events (TEAE), no TEAEs resulted in permanent treatment discontinuation, and no patient died. These data support the positive clinical impact with use of 40 mg/kg qow avalglucosidase alfa in patients with IOPD, the most severely affected population of patients with Pompe disease. Funding, Sanofi Genzyme.

doi:10.1016/j.ymgme.2020.12.128

123

The Mucopolidosis Collaborative Research Network (MCRN)

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Mucopolidosis alpha-beta is a complex multisystem lysosomal disease caused by mutations in *GNPTAB*, the gene encoding N-acetylglucosamine-1-phosphotransferase. This transmembrane enzyme catalyzes the formation of mannose 6-phosphate (M6P) moieties to N-linked glycans of soluble acid hydrolases. This posttranslational modification is required for receptor-mediated targeting of the hydrolases to lysosomes. Due to the ultra-rare status of Mucopolidosis and lack of recombinant enzyme as a basis for treatment, therapeutic development has seen limited progress despite substantial advances in the understanding of disease pathogenesis. To overcome this impediment the Mucopolidosis Collaborative Research Network (MCRN) was formed in 2019 by a highly cross-disciplinary team to uncover and implement

viable therapeutic options for this underserved group of patients. The MCRN is dedicated to an open, collaborative, and confidential pursuit of research objectives that combines diverse scientific and medical expertise worldwide. Collaboration within the Network allows participants to share focused expertise that reduces duplication of efforts while driving efficiency and cost-savings. Our goal is to coordinate research efforts, engage the patient population, and raise awareness among sponsors. Membership comprises principal investigators from over half a dozen locations and multiple patient advocacy groups. The membership is balanced by gender and includes individuals at all stages of their careers. Disciplinary expertise is represented in the areas of structural and functional biochemistry, cell and developmental biology, molecular genetics, medical genetics, comparative genetics, interventional genetics as well as other clinical specializations within human and veterinary medicine. The patient foundations bring decades of fund development experience alongside patient advocacy expertise. The MCRN is focused on the evaluation of potential therapeutic approaches for the *GNPTAB*-related disorders, with ongoing efforts in the United States and Europe to elucidate and implement potential therapies in model systems, and to gain a better understanding of what may be achievable as a translational therapeutic.

doi:10.1016/j.ymgme.2020.12.129

124

New insights into GI manifestations in late-onset Pompe disease: Lessons from the bench and bedside

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There is growing evidence of smooth muscle involvement in Pompe disease with reports of life-threatening basilar artery and ascending aorta aneurysms, difficulties in swallowing and speech, and gastrointestinal (GI) involvement. We studied the histopathology of the GI tract in Pompe mice (GAAGO 6^{neo}/6^{neo}), and impact of enzyme replacement therapy (ERT) with alglucosidase alfa. We evaluated adult patients with late-onset Pompe disease (LOPD) using Patient-Reported Outcomes Measurements Information System - Gastrointestinal (PROMIS-GI) symptom scales, and a GI-focused medical history. Pompe mice showed extensive and progressive glycogen accumulation in the smooth and striated muscles throughout the GI system (from tongue to rectum), and in the Aurbach's plexus, as early as age 3 months. Long-term (6 months) enzyme replacement therapy (ERT; 20 mg/kg biweekly, age at initiation 2 months) was more effective to clear the glycogen accumulation than short-term (5 weeks) ERT (20 mg/kg weekly, age at initiation 3 months) in Pompe mice. We enrolled 58 patients with LOPD (median age: 51.55 \pm 15.5 years, range: 18–79 years; 35 females; 53 on ERT, 4 ERT naïve, 1 off ERT for 3 years; median duration of ERT: 5.5 years; range: 2 months–13 years). The PROMIS-GI (cross-sectional) data from 52 patients suggested a high prevalence of gas/bloating (98%), reflux (94%), constipation (84%), diarrhea (72%), belly pain (68%), nausea/vomiting (61%), disrupted swallowing (54%), and bowel incontinence (40%). Onset of GI symptoms ranged from childhood to seventh decade of life. Longitudinal data ($n = 19$, followed over 16 months) revealed that most patients had either no change or worsening GI symptoms over time, even after ERT initiation. This study sheds light on the significant disease burden caused by GI manifestations. Clinicians should evaluate GI manifestations during routine clinical visits, and use quantitative tools such

as PROMIS-GI measures. The study also highlights the need for next generation therapies that target the smooth muscles.

doi:10.1016/j.ymgme.2020.12.130

125

Report of the first Brazilian patients with MPS IIID, with the observation of an unexpected increase of di-sulfated keratan sulfate

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Mucopolysaccharidosis type IIID (MPS IIID) or Sanfilippo syndrome type D is caused by a deficiency of the lysosomal enzyme *N*-acetylglucosamine-6-sulfatase. Among the four subtypes of Sanfilippo syndrome, this is the least frequent.

Objective

To investigate two patients with clinical suspicion of mucopolysaccharidosis type III, in whom the more common types IIIA, IIIB, and IIIC were previously excluded. Material and methods: Blood and urine were collected for biochemical tests (enzyme assays, total glycosaminoglycans - GAGs - measurement by dimethylmethylene blue - DMB - colorimetric method, identification of GAGs species by electrophoresis, and quantitation of specific GAGs by liquid chromatography/tandem mass spectrometry-LC/MS/MS) and molecular analysis by next-generation sequencing using a customized panel which includes the *GNS* gene. A few other sulfatases were assayed to exclude multiple sulfatase deficiency. Age-matched controls were used for the quantitative measurements of GAGs.

Results

The two patients had a deficient activity of *N*-acetylglucosamine-6-sulfatase (0.55 and 2.2 nmol/24 h/mg of protein; normal range: 7–22) in leukocytes. Increased levels of total urinary GAGs (374 and 404 µg/mg of creatinine; normal age-range: 67–124) were detected by DMB assay, and the presence of heparan sulfate in urine was observed in the electrophoresis. LC/MS/MS of urinary GAGs revealed high levels of heparan sulfate (HS-0S: 32 and 1.43 ng/mg of creatinine [average age-matched controls: 0.28 ng/mg of creatinine], HS-NS: 7.7 and 0.45 ng/mg of creatinine [average age-matched controls: 0.12 ng/mg of creatinine]). Di-KS was also elevated in both patients (0.8 and 2.36 ng/mg of creatinine [average age-matched controls: 0.23 ng/mg of creatinine]). NGS identified the following genotypes: c.624 + 1G > T/624 + 1G > T and c.1120_1122dup/1120_1122dup in the *GNS* gene, respectively.

Conclusions

To the best of our knowledge, we are reporting the first Brazilian patients with MPS IIID. Di-sulfated keratan sulfate also might be a

useful marker for MPS IIID, although further samples should be analyzed to confirm this observation.

doi:10.1016/j.ymgme.2020.12.131

126

Screening for Niemann-Pick disease type C in Latin American using Lyso-SM-509 measurement in dried blood spots

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Introduction

Niemann-Pick type C (NPC) disease is an autosomal recessive lysosomal disorder of cholesterol trafficking that leads to several manifestations, including progressive neurodegeneration. Lyso-sphingomyelin-509 (Lyso-SM-509) has been identified as a very sensitive and specific biomarker for NPC.

Objective

To investigate the feasibility of a screening program for NPC in Latin America based on Lyso-SM-509 measurement and sequencing of the *NPC1* and *NPC2* genes.

Material and methods

Dried blood spots (DBS) were collected from patients with suspected NPC in four Latin American countries for measurement of Lyso-SM-509 by liquid chromatography tandem mass spectrometry, followed by molecular analysis of *NPC1* and *NPC2* genes by next-generation sequencing (NGS) when Lyso-SM-509 was increased.

Results

A total of 92 dB samples was collected, being 61 from Brazil, 27 from Colombia, 3 from Ecuador, and 1 from Bolivia. Eight samples had levels above the cutoff of 3321 nmol/L. These samples were referred for genotyping, and results in 5 patients are already available, all of them showing pathogenic variants in the *NPC1* gene: p.Ala1035Val/Val694Leu, p.Gln710fs/Gln710fs, p.Phe1221fs/Ala1035Val, and two patients were homozygous for p.Ala1035Val. The average level of lyso-SM-509 in the patients with NPC was 11,403 nmol/L (range: 3819–22,747), while in the unaffected subjects was 1351 nmol/L (range: 333–2716). The average age at diagnosis was 2.9 years (range: 5 months to 10.5 years).

Conclusions

Although results are still preliminary, Lyso-SM-509 seems to be a reliable marker for the screening of NPC. The possibility of doing both Lyso-SM-509 and NGS in a DBS sample transported at room temperature is a very convenient alternative for the identification of NPC patients in a region like Latin America, with large distances to be covered and many borders to be crossed. (This work was possible due to the collaboration of medical doctors from Brazil, Colombia, Ecuador and Bolivia, and the support of Janssen Pharmaceutica.)

doi:10.1016/j.ymgme.2020.12.132