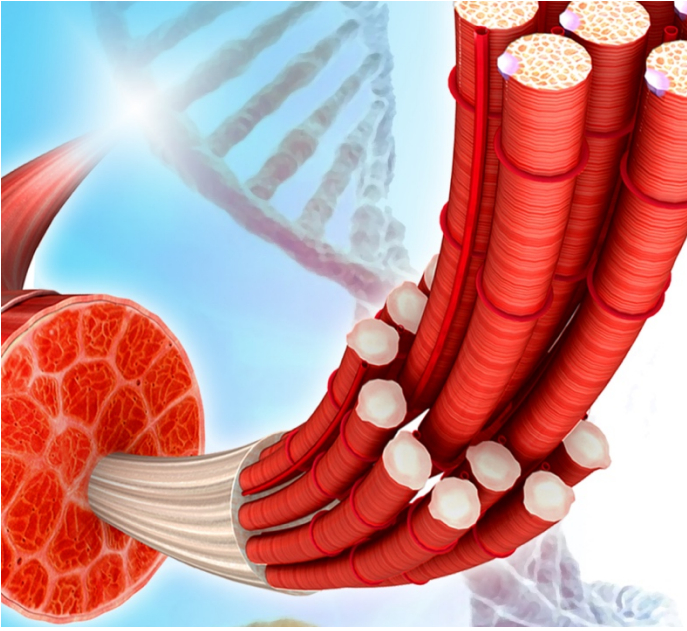

MOVING FORWARD IN POMPE DISEASE:

Optimizing Outcomes in the Era of Next-Generation Therapies and Advanced Newborn Screening

Frequently Asked Questions

1. How variable is the presentation of late-onset Pompe disease (LOPD) in the early ages of life?

Patients with LOPD have a broad phenotypic spectrum where symptoms can present as early as in the first year of life to as late as the sixth decade of life. Patients with LOPD typically have at least 1 IVS splice-site mutation (c.32-13T>G), which is the most common pathogenic variant seen in LOPD. Patients, especially children, do experience diagnostic delays, which can be longer than 12 years. Newborn screening (NBS) with careful monitoring will help reduce these diagnostic delays. NBS is also helping clinicians gain a greater understanding of the natural history of LOPD.

2. When would you use muscle ultrasound to evaluate patients with LOPD who were identified by NBS and are not yet symptomatic?

Quantitative muscle ultrasound measuring echo intensity correlates well with creatine kinase (CK) levels and motor assessment tools in patients with LOPD. Dr. Kishnani believes that muscle ultrasound can be a helpful monitoring tool for “asymptomatic” patients with LOPD identified by NBS. Early involvement of the quadriceps, thoracic paraspinals, and tibialis anterior (including the medial gastrocnemius) has been observed and is similar to the pattern of involvement seen in adults with LOPD. Dr. Kishnani is using quantitative muscle ultrasound at the time of initial assessment and as a monitoring tool. This is in addition to a good clinical and developmental evaluation, including neuromuscular evaluation and physical therapy assessments. Additionally, CK and urine glucose tetrasaccharide (Hex4) biomarkers must be monitored.

3. What types of LOPD mutations are associated with early abnormal kinematic features?

Much remains to be learned about early abnormal kinematic features and the associated genotypes in patients with LOPD. However, Dr. Kishnani has observed that even patients who are compound heterozygotes with an IVS splice-site mutation and a second pathogenic variant, such as a frameshift or missense or nonsense mutation, can exhibit early kinematic concerns.

4. **Are there similarities in the phenotypes of siblings with LOPD who have the same genotype?**

There is a lot of phenotypic heterogeneity in patients with LOPD, even amongst siblings who carry the same genotype. Some patients may primarily have musculoskeletal features whereas others may have more of a pulmonary presentation. Also, the degree of involvement and rate of progression is variable between siblings. Patients with LOPD identified via NBS could have older siblings, or in rare instances even parents, who are affected. Enzymology testing, which is relatively cheap, can be performed in these relatives to identify whether these individuals are affected or are carriers. If the enzymology levels are in the carrier range, then targeted mutation analysis, which is more expensive, can be performed.

5. **Would you treat a patient with only gross motor delays who had normal Hex4 and CK levels and a biopsy that showed no changes empirically with enzyme replacement therapy (ERT)?**

Patients with only gross motor delays and no other signs of Pompe disease (PD) progression should be evaluated for other causes of their symptoms. Patients need to have evidence of disease involvement prior to initiating ERT. However, patients can experience disease progression while exhibiting normal CK or urine Hex4 levels. In the setting of LOPD, glycogen can be intra-lysosomal and, in such situations, urine Hex4 can be normal. Additionally, approximately 5% of patients with LOPD can have normal CK levels. This is why a holistic approach is necessary for evaluating and managing patients with PD.

6. **Why is there a plateau effect over time with first-generation ERT?**

First-generation ERT is lifesaving and has allowed babies with infantile-onset PD (IOPD) to survive; the oldest treated patients are now in their second decade of life. However, the limitation of first-generation ERT is that it is poorly phosphorylated resulting in limited targeting to the skeletal muscle. The first-generation enzyme can clear some glycogen, but it is unable to clear all residual glycogen in the skeletal muscle. In general, next-generation ERTs can clear more glycogen because of greater numbers of mannose-6-phosphate (M6P) tags enabling better tissue uptake and especially lysosomal targeting of the recombinant enzyme. In the COMET and PROPEL studies, patients who had received first-generation ERT showed a further decrease in urine Hex4 and CK after switching to next-generation ERTs, indicating a greater ability to clear glycogen. These patients also showed improved clinical response in measures, such as 6-minute walk test, forced vital capacity % predicted, maximal inspiratory pressure, maximal expiratory pressure, and quality of life measures.

7. **Are there concerns about cross-reacting antibodies when switching from first-generation to second-generation ERTs?**

Based on data from the COMET clinical trials, including MINI-COMET, and emerging real-world evidence, patients who had low antibody titers continued to have low antibody titers after switching ERTs. Regardless of these data, antibody monitoring should occur every 2 months for the first 6 months when a patient is initially switched to a second-generation ERT to determine whether a patient is mounting an antibody response. In patients without an increase or with low antibody titers, the time between antibody testing can be increased to every 6 months. Alglucosidase alfa and avalglucosidase alfa are similar and, as such, there is a lot of cross reactivity between the 2 products. The difference is a greater number of M6P tags with avalglucosidase alfa. Overall, patients who are treatment naive or switch from alglucosidase alfa to avalglucosidase alfa should expect a similar profile. In patients with high

antibody titers to alglucosidase alfa, they will also likely have high titers against avalglucosidase alfa.

8. Why is avalglucosidase alfa not approved for treatment of IOPD in the United States?

Avalglucosidase alfa is approved across the PD continuum in Europe. In the MINI-COMET clinical trial, patients with IOPD were switched from alglucosidase alfa to avalglucosidase alfa. These patients exhibited clinical decline or a suboptimal response to alglucosidase alfa at the time of ERT switching; none were treatment naive. As such, there is limited knowledge at this time about the experience of avalglucosidase alfa treatment in very young babies with IOPD. BABY-COMET is a clinical trial that is evaluating the treatment of avalglucosidase alfa in treatment-naive babies with IOPD. The study is currently ongoing. The US Food and Drug Administration is likely awaiting safety and efficacy results in this study.

9. What is the long-term ERT experience for patients with IOPD and LOPD?

Patients require a careful approach to timely intervention because starting ERT in patients who are younger than 1 year means a lifetime of treatment. This is a big decision. The oldest patients with IOPD treated with ERT are now in their mid-20s. Dr. Kishnani has observed some white matter hyperintensity changes on brain MRI. In patients with the greatest amount of hyperintensity changes, there is some evidence of neurological and cognitive involvement. There are many individuals with IOPD that are in college and have jobs, telling us that even in IOPD there is a broad spectrum of disease.

For symptomatic patients with LOPD who have been identified by NBS, it is important to start treatment early to optimize long-term outcomes. Many families believe that symptoms will plateau after a few years of treatment; however, this is likely the situation in patients who started treatment later in the course of their disease. Now the goal is to start treatment ahead of significant clinical decline since more robust screening tools and therapeutic options are available. However, families do need to be given time to process and consider the implications of ERT because it is a lifelong therapy.

At the same time, there is no reason to start treatment in patients with LOPD who are asymptomatic and may never show symptoms. Additionally, some patients with subtle features may do well with physical therapy or interventions other than ERT. Clinicians must be cautious when deciding who needs to be on ERT and who does not.

10. What are therapies are being studied to address the motor neuron symptoms of PD?

Groups are studying ERTs that cross the blood brain barrier and gene therapies with an attempt to target the central nervous system.