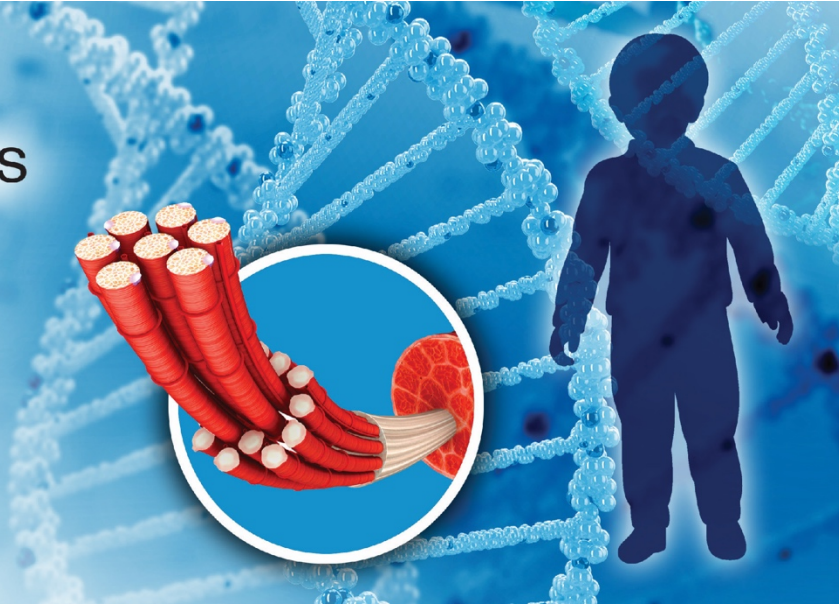
Exploring Next-generation Therapies to Mitigate Disease Progression in POMPE DISEASE



Frequently Asked Questions

1. What types of imaging can be used to assess the severity of Pompe disease (PD) in the muscles of children?

Magnetic resonance imaging (MRI) has been used to assess muscle involvement and the extent of muscle damage in PD. However, it is not a practical tool in children due to the length of time needed to complete the imaging, the lack of comfort felt by children during imaging, and the frequent need for sedation. MRI can be used in children starting around 6 years of age because there are available data for normal values at that point. Muscle ultrasound is emerging as a useful tool to assess muscle involvement in neuromuscular diseases; it is inexpensive, images can be acquired in a shorter amount of time than with MRI, and there is no need for sedation. Increases in echo intensity suggest muscle degeneration because a correlation exists between increasing echo intensity and the amount of fibrofatty tissue within muscles as seen on biopsy. Published data show that worsening muscle ultrasound findings correlate with increases in aspartate aminotransferase and creatine kinase, in addition to diminished function on physical therapy assessments in adult patients with late-onset PD (LOPD).

2. What cardiac findings are associated with LOPD?

By definition, LOPD is distinguished from infantile-onset PD (IOPD) by the absence of cardiomyopathy in the first year of life. Sufficient residual enzyme activity is present in patients with LOPD and it appears to be cardioprotective. Typically, patients with the common leaky intervening sequence (IVS) splice-site mutation do not develop cardiomyopathy; however, these patients can develop rhythm disturbances. Patients with LOPD, such as those identified in Taiwan, China, and India, do not typically carry the IVS splice-site mutation. These patients can develop left ventricular hypertrophy (LVH) if left untreated. Cardiac findings, such as LVH, heart rhythm disturbances, and, in rare instances a dilatation of the root of the aorta, can present at different timepoints (ie, very early or later in life or not at all). Therefore, careful monitoring of these patients is important.

3. Are antidrug antibodies problematic for both IOPD and LOPD?

Immune tolerance induction (ITI) is now considered the standard of care for patients who are cross-reactive immunological material (CRIM)-negative. Approximately one-third of patients with IOPD who are CRIM-positive also develop high and sustained antibody titers; therefore, it is important to monitor these patients.

The number of patients with LOPD who develop antidrug antibodies is still unknown. By default, patients with LOPD are CRIM-positive because they have some residual enzyme activity. However, patients with LOPD who are receiving enzyme replacement therapy (ERT) should have antibody titers routinely assessed because these individuals can also develop high and sustained antibody titers against the drug. Dr. Kishnani does believe that high sustained antibody titers can affect enzyme uptake and negatively impact patient outcomes over time. Patients with LOPD and high sustained antidrug antibodies have undergone successful ITI and shown improvements in biomarkers and other functional measures.

4. Should patients with LOPD who begin to develop motor delays be treated?

According to Dr. Kishnani, late onset does not mean late presentation. LOPD can present early in infants. Once muscle damage has occurred, it is difficult to reverse that damage. While not every baby with LOPD identified by newborn screening will require treatment, treatment should begin once symptoms are detected. These patients can present with clinical delays that are overlooked if patients are only assessed using functional measures, such as the Alberta Infant Motor Scale. Thus, kinematic and postural assessments by a physical therapist with expertise in neuromuscular diseases are important. Finally, treatment can consist of physical therapy or other strategies to address symptoms, as well as ERT. Treatment initiation must be individualized to each patient, and patients must be evaluated carefully to detect early signs and symptoms of disease progression.

Dr. Toscano agrees with Dr. Kishnani's viewpoint because newborn screening has created a gray area in the management of patients with LOPD. Some patients with LOPD do not show disease involvement and therefore should not be treated. Dr. Toscano recommends clinicians regularly evaluate patients and begin treatment when there is evidence of muscle degeneration, even if the patient's clinical symptoms are mild.

Dr. Schoser suggests a new type of monitoring algorithm is needed that includes more measures. Clinical elements and biomarkers should both be considered when making management decisions. Imaging guidelines also need to be developed and included to make more informed decisions around treatment.