POMPE Connections

Medical progress in Pompe disease

In 1932, JC Pompe, a Dutch pathologist, described a 7-month-old infant with a greatly enlarged heart who had died shortly after being admitted to the hospital. This was the first mention of the disorder that later became known as Pompe disease. Thirty years later, a scientist in Belgium discovered that people with Pompe disease were missing an enzyme called ***acid alpha-glucosidase****, or* ***acid maltase.*** *This enzyme is normally found inside a compartment of the cell called the* ***lysosome.*** *Like all enzymes, acid alpha-glucosidase has a specific job to do. It helps break down glycogen, a form of sugar that is stored in muscle cells and released when the body needs energy. Without the enzyme, glycogen builds up in the cells and weakens muscles throughout the body.*

Ever since the link between acid alpha-glucosidase and Pompe disease was discovered, researchers around the world have been searching for ways to replace the missing enzyme. Though we do not yet have a cure for Pompe disease, progress in developing enzyme replacement therapy and gene therapy has raised hopes that effective treatment will soon be available. This handout describes the medical advances that are moving us closer to the day when an approved treatment can be offered to everyone with Pompe disease.

Q What is enzyme replacement therapy? How can it help people with Pompe disease?

A With enzyme replacement therapy (ERT), people with Pompe disease are given a special form of acid alpha-glucosidase to replace the missing enzyme. This special form, called *rhGAA,* is made in genetically engineered mammalian cells (a way of making enzymes of the highest quality in the large amounts necessary for ERT). The therapy is given **intravenously** (injected directly into the bloodstream) so that it can reach the muscles and break down the glycogen that causes damage when it builds up in the cells. While ERT is not a cure for Pompe disease, it may slow the progression of muscle weakness and improve muscle function. ERT is a long-term treatment that is given at regular intervals (for example, once a week or twice a month). The dose is based on the patient's weight.

Clinical trials to study the safety and effectiveness of ERT began in 1999 with a small number of severely affected infants, 2 teenagers, and 1 adult. These trials showed that ERT can have great benefit, especially when started early in the course

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Other names for Pompe disease

Acid alpha-glucosidase deficiency, acid maltase deficiency (AMD), glycogen storage disorder (GSD) type II, glycogenosis II, and lysosomal alpha-glucosidase deficiency. In different parts of the world, Pompe may be pronounced *"pom-PAY," "POM-puh,"* or *"pom-PEE."*

of the disease. The infantile-onset patients in those early trials showed major improvements in heart muscle function. A number of patients gained skeletal muscle function as well. Some of the infantile patients started on ERT are even walking independently. It is important to add, though, that once muscles are severely damaged, they cannot fully regain function.

Although ERT for Pompe disease has not yet been approved, more than 100 patients around the world are now receiving the therapy through clinical trials and expanded access programs. These programs allow severely affected patients to receive ERT before the therapy is approved for wider use. For information about enrolling in clinical trials, see *Where to learn more* on page 4.

Q **What is gene therapy? How can it help people with Pompe disease?**

A The goal of gene therapy is to replace the defective gene that makes acid alpha-glucosidase by giving the body the genetic information it needs to start making normal enzyme. This could lead to a cure for Pompe disease, but research on gene therapy is still at an early stage. One of the biggest challenges is finding a way to transfer the gene into the muscle cells. Researchers have had some success using different strains of a common cold virus to transfer the gene into mice and quail. In both animal models, the virus reached the liver where it started producing the enzyme and sending it out to muscle cells through the bloodstream. Within days, the enzyme started clearing away the glycogen and improving muscle function. More studies are needed to evaluate the safety and effectiveness of this approach before it can be tried in humans. To find out how gene therapy research is progressing, see *Where to learn more* on page 4.

Q **Is bone marrow transplantation an option for treating Pompe disease?**

A Bone marrow is the soft tissue inside the bones where new stem cells are produced. Normal stem cells are capable of creating new cells that contain the enzyme missing in people with Pompe disease. Bone marrow transplantation, or BMT, is a way to replace bone marrow stem cells that do not have enough of the enzyme with normal stem cells that will supply acid alpha-glucosidase to the muscles. This approach has been tried but has not yet been successful.

Q **What is the process for developing new treatments?**

A The process for developing new treatments starts in the laboratory where researchers begin to test their theories. This is followed by animal studies and, if these go well, by research studies in humans called *clinical trials*. The purpose of these studies is to gather information about the safety of the therapy and how

well it works. It takes many years of strict and careful testing before an experimental treatment is approved for use in humans.

Clinical Trial Phases:

Clinical trials are done in 4 stages, or phases. A study plan, called a protocol, spells out the goals of each phase of the trial.

- **In phase 1**, the experimental treatment is given to a small group of volunteers to learn about safety issues such as side effects and dosing
- **In phase 2**, the treatment is given to a larger group of affected people to see how well it works and learn more about safety. If phase 2 trials are promising, the study is expanded to a larger number of medical centers in phase 3
- **A phase 3** trial for Pompe disease might enroll 50 or 60 patients and would yield a much broader picture of how the treatment affects people with the disease
- **Phase 4** studies are usually done after the treatment is approved to obtain more information about its risks, benefits, and effectiveness when combined with other therapies

To learn more about the clinical trial process, visit www.clinicaltrials.gov.

Q **What are the benefits and risks of participating in a clinical trial?**

A

For rare disorders like Pompe disease, taking part in a research study may give patients access to experimental treatments that could improve, save, or extend their lives. Expanded access programs could provide ERT to patients with more severe disease who might not otherwise qualify for a clinical trial. Randomized studies that enroll larger numbers of patients (but assign them to different groups to compare treatments) could give people with less severe disease the chance to begin ERT before muscle weakness has progressed beyond mild disability. Because your health is closely monitored, enrolling in a clinical trial also gives you access to medical care from experts in Pompe disease.

Before deciding to participate in a clinical trial, it is important to weigh the possible risks as well as the benefits. Read the protocol and talk with your healthcare provider (or your child's healthcare provider) to get a better idea of your chances for being accepted into the trial and how long it might be before you could start treatment. Think about how taking part in the trial could affect your health, your family, your job, and anything else that matters to you. Be sure to ask what kind of support would be available to you if you decide to enroll (for example, will any of your expenses be covered if you have to travel some distance to be treated?). If you have questions about ERT trials for Pompe disease, contact the Medical Information department at Genzyme, the company sponsoring the research (see *Where to learn more* on page 4).

Q **How can I find out about clinical trials that are going on in my area?**

A To learn about clinical trials worldwide that are now recruiting patients with Pompe disease, visit www.clinicaltrials.gov (a service of the US National Institutes of Health) and enter "Pompe" in the search area. You can get more information by contacting the International Pompe Association (IPA) or other groups listed in *Where to learn more* below.

Where to learn more

These sources can help you keep up with the research developments and treatment advances for Pompe disease:

- The **International Pompe Association (IPA)** publishes frequent updates on clinical trials and treatment studies for Pompe disease. Visit the IPA Web site at www.worldpompe.org and click on "Latest News." Also find links to research articles on gene therapy and enzyme replacement therapy (ERT), summaries of IPA conferences, and first-hand accounts from patients and parents of young children who have taken part in clinical trials for ERT
- The **Genzyme Medical Information** department can answer specific questions about enrolling in ERT clinical trials for Pompe disease. In the United States, call 1-800-745-4447 or e-mail medinfo@genzyme.com. In Europe, call 31-35-699-1499 or e-mail eumedinfo@genzyme.com. Outside of the United States and Europe, call 1-617-768-9000
- The **Pompe Center at Erasmus University** in the Netherlands seeks to improve understanding of Pompe disease by sharing research and treatment advances through its Web site at www.pompecenter.nl. The Web site has links to Pompe disease support groups and neuromuscular disease research centers throughout the world
- The **Pompe Community** Web site sponsored by Genzyme offers information on ERT and Pompe disease at www.pompe.com
- The **Pompe's Group of the Association for Glycogen Storage Disease (AGSD-UK)** is a patient group that supports research on Pompe disease and promotes awareness of advances in treatment through a Pompe disease session at the annual AGSD conference, as well as newsletters and research updates that are posted on the Pompe's Group Web site at www.pompe.org.uk