enzyme replacement therapy for

FABRY DISEASE

AT THE EMORY LYSOSOMAL STORAGE DISEASE CENTER

www.genetics.emory.edu

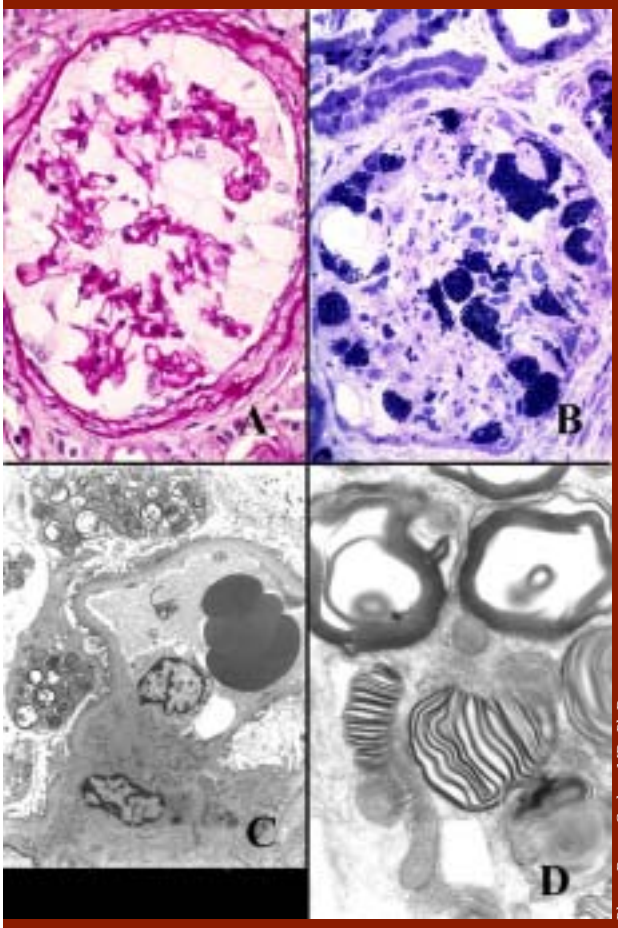


Photo: Byron Croker, MD, Ph.D

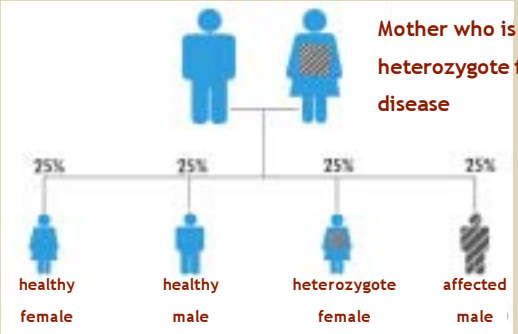
EMORY UNIVERSITY

DEPARTMENT OF HUMAN GENETICS • DIVISION OF MEDICAL GENETICS • EMORY UNIVERSITY SCHOOL OF MEDICINE • ATLANTA, GEORGIA

What is Fabry disease?

Fabry disease (FD) is an X-linked genetic disease caused by a deficiency of the enzyme α-galactosidase A (α-Gal A) in the body. The enzyme α-Gal A's function is to break down a fatty substance called globotriaosylceramide (or GL3). When α-Gal A is absent, GL3 builds up in the blood vessel walls throughout the body. As the abnormal storage of GL3 increases with time, the body's blood vessels become narrowed, leading to decreased blood flow and under-nourishment of the tissues. This abnormal process occurs in blood vessels throughout the body, particularly those blood vessels in the skin, kidneys, heart, brain and nervous system. The early symptoms of Fabry disease, which usually begin in childhood, include decreased sweating, heat intolerance, proteinuria, a reddish-purple skin rash (angiokeratoma), severe pains in the hands and feet, hearing loss, chronic fatigue, and gastrointestinal issues such as chronic diarrhea. Fabry disease symptoms affect both women and men. Since the disease is progressive, if left untreated Fabry disease results in many severe health problems such as kidney failure, heart problems including enlargement of the left side of the heart (left ventricular hypertrophy) and valve disease, and cerebrovascular problems such as stroke and vertigo. Not every person with Fabry disease will have all the same symptoms of disease progression; however, the disease always gets worse over time. [1]

Possible combinations in the children: there is a 1 in 2 chance (50%) for each child to inherit the Mother's gene for Fabry disease



What is enzyme replacement therapy (ERT)?

The term Enzyme Replacement Therapy (or ERT) refers to a treatment using an enzyme produced by genetically engineered cells. The purpose of ERT is to replace the enzyme that a person with Fabry disease cannot make on his or her own. In Fabry disease, the enzyme is infused into the vein by IV every other week and taken up by the cells. Once it enters the cells, the enzyme can remove the stored GL3 and improve cellular function. This should stop GL3 from building up and hopefully stop or slow the progression of Fabry disease symptoms and health problems. The therapy has to be given every two weeks because the infused enzyme is used up by the body quickly. In Fabry disease the ERT medication options are agalsidase beta (also called Fabrazyme®) and agalsidase alfa (also called Replagal®) (Note that the FDA has not approved Replagal for use in the U.S. at this time). ERT is the only treatment that addresses the underlying cause of Fabry disease.

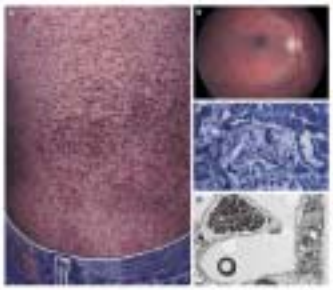
How safe is ERT?

Multiple research studies have looked at the safety of ERT before and after it was approved by the United States Federal Food and Drug Administration in 2003 and found it to be safe for human use. In these studies, the individuals given ERT had fewer serious Fabry related health problems than the individuals who were not on ERT. This tells us that the ERT did not harm individuals with Fabry disease in the study. [1] While ERT is a safe therapy, individuals treated with ERT can have infusion reactions. These reactions are not life threatening and are most often controlled by decreasing the speed of the infusion and giving medications. The most commonly occurring reactions were fever and shaking.

How effective is ERT?

Research studies have shown that ERT, when given at 1 mg/kg dose every other week by intravenous infusion, reduces the amount of GL3 in urine, plasma, kidney cells, skin cells, and heart cells. One trial showed that at 11 months of treatment every other week, 94-96% of patients had no GL3 in kidney cells (renal and interstitial) on kidney biopsy, 85% of patients' heart cells (myocytes) were clear of GL3, and all of patients' skin cells from skin biopsy were clear of GL3. Over the course of 35 months, patients on ERT were 61% less likely to have an event (kidney failure, heart attack, stroke, or death) than untreated patients. Treatment effect was most pronounced in patients treated early in their disease. [1]

When the amount of GL3 is reduced in the body, the disease should stop progressing and in some cases reverse. However, depending on the stage of Fabry disease, irreversible damage may have already been done to some organs. For example, if an individual is already in end stage renal disease, the ERT cannot stop kidney failure, but can hopefully increase the time until kidney failure, and reduce the chance for complications related to cardiac and strokes. In addition, for an individual who has had strokes, the hope is that the ERT will help prevent future strokes, heart attacks, and kidney disease. More research into the effectiveness of ERT and damaged organs is still needed.



Angiokeratomas on the back, tortuous retinal arterioles, renal biopsy stained to show inclusions, and electron microscope examination showing lysosomes containing glycolipid, in a young man with Fabry disease.

Taken from: NEJM 349 (21): 10, Figure 1, November 20, 2003

How do I pay for ERT?

In most cases, health insurance covers the ERT and infusions. Genzyme, the company that makes Fabrazyme, has a program called Genzyme Treatment Support (800-745-4447) that will work with you and the Emory Lysosomal Storage Disease Center to obtain precertification and ongoing coverage for ERT while maintaining your insurance for Fabry Disease and other health conditions. If you do not have health insurance, there are several programs including Genzyme Treatment Support (GTS), the Genzyme Charitable Access Program (CAP), Patient Services Incorporated (PSI), and the Fabry Support and Information Group (FSIG) which will assist you in getting ERT. By working closely with these programs, everyone who needs ERT should be able to obtain treatment.

Should I still go to specialists and have monitoring tests when I am on ERT?

Yes. ERT is only part of the treatment of Fabry disease. You still need monitoring tests to watch for any health problems and to see specialists to treat any problems that arise. You still need to take any medications prescribed by your physicians. Your lysosomal storage disease center and your physicians will help you determine which tests, medications, and specialists you need.

When should ERT begin?

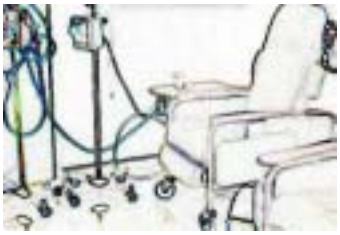
As early as possible. Early intervention with ERT offers the best protection against the complications and health problems of Fabry disease. In adults, this means beginning ERT as soon as Fabry Disease is diagnosed. In children with Fabry Disease, the decision to begin therapy is based on the symptoms that they have and discussions of the risks and benefits of ERT with your Fabry Disease specialist.

How long do you have to stay on ERT?

ERT is a life-long treatment. As soon as ERT is stopped, the GL3 begins accumulating again. When this happens, the Fabry symptoms and damage will progress again.

What happens if you stop ERT?

There are not any detailed studies available that can tell us exactly what happens when you



stop ERT. We do know that as soon as ERT is stopped, the GL3 levels begin accumulating. Specific information on how long it takes the GL3 to build up to previous levels in not available in FD patients. Studies looking at another lysosomal storage disease, Gaucher disease, found that when ERT is stopped, the storage products built up quickly in most individuals. Those individuals had a quick regression to the same symptoms they had before beginning ERT. When restarting ERT, it took time to return back to the healthy levels they reached on ERT before stopping. [2]

Is ERT beneficial in individuals after a kidney transplant?

Small scale studies of individuals indicate that ERT is safe and effective against non-kidney related complications of Fabry disease. In one small study of three kidney transplant patients treated with ERT at a dose of 1 mg/kg every 2 weeks for 13-18 months, the plasma GL3 decreased (in all 3 patients), extremity pain resolved in the one patient experiencing pain, and cardiac problems were stabilized or improved in 2 out of 3 transplant patients studied. [3]

What is a Port-A-Cath® and should I get one for my infusions?

A Port-A-Cath® is a combination of a port and an intravascular device used to obtain intravenous access in the same spot for infusions like ERT. The device is located under the skin in the upper part of the chest and connected into a large vein. Surgery under general anesthesia is required to place the Port-A-Cath®. The Port-A-Cath® is not required for infusions, but the benefit of the Port-A-Cath® is that it allows for an easy access to a vein for infusions. The downsides include: Port-A-Caths® are placed through surgery which requires general anesthesia, there is a risk of infection with the Port-A-Cath®, and although Port-A-Caths® can last for years they may need to be replaced or removed sooner. The decision to get a Port-A-Cath® is a personal choice that should be discussed with your physician.

Do I need to do anything special for my first infusion?

Please drink plenty of water the night before and the morning of your infusion. Being well-hydrated makes starting the IV for the infusion line much easier. Note, if you are on dialysis or have another reason for careful fluid intake monitoring, continue to follow your doctor's instructions. The morning of the infusion eat breakfast as normal and prepare for a long day.

What happens during an infusion?

The first infusion takes approximately 4-5 hours of actual infusion time and 1 hour after the infusion has ended for monitoring. You may wish to bring books, a laptop computer, cell phones, etc. A guest/family member/friend may accompany you for your infusion if you wish. You may bring your own lunch, or have a guest pick up lunch for you during the infusion. Please note that if you are infused within a cancer infusion center, they may have restrictions on hot or strongly smelling foods. Otherwise, you may eat/drink during the infusion as you wish. **Before leaving your infusion, make sure to schedule your next infusion. Your infusions should be scheduled every other week**.

What are possible infusion related problems or reactions I should watch for?

The most common problems during an infusion are:

Cold	Headache	Fever	Breathlessness	Chest Pain
Chills	Nausea	Itching	Racing Heart	Hives or bumps

If you have any of these or any other symptoms, tell your infusion nurse immediately. In most cases, your infusion rate will be slowed significantly or stopped until the symptoms are gone. You may also be given Ibuprofen or Benadryl in order to manage these reaction symptoms. Once your symptoms have subsided, the rate of your infusion will gradually be increased. If

information about infusions

symptoms continue, we can change pre-medications and the infusion rate to stop infusion problems. Please contact us at 404-778-8565 or 800-200-1524 to discuss any infusion related problems you are having or are worried about.

What if I have any unusual symptoms after the infusion?

If you feel any symptoms such as increased leg pain, headache, increased tiredness, chest pain, racing heart, chills, nausea, fever, or itching in the days following your infusion, please notify your physician and/or treatment coordinator immediately. If you are followed by the Emory Lysosomal Storage Disease Center, contact us at 404-778-8518 or 800-200-1524 during work hours (9am to 5 pm) or the Medical Geneticist on Call, Pager: 404-701-0532 after hours.

What if I have to miss an infusion?

Please contact us immediately if you are unable to attend one of your scheduled infusion dates. If you are unable to attend an infusion, we will try and reschedule your infusion within 7 days. Infusions should be given 14 days apart, but a makeup infusion can be fit in 7 days before the next infusion. If you find that you are missing multiple infusions, talk to us to discuss the problems you are having making infusions so that a solution can be found.

When can the infusion nurses increase the speed of my infusion?

If you reach the 7th infusion and haven't had any problems, then Emory and your infusion nurse may be able to begin slowly increasing the infusion by 5 mg/hour on the 8th infusion. Every infusion after that we will increase the rate by 5 mg/hour until the infusion time is two hours. If you have an infusion related reaction, the time of infusion will be increased and the speed of the infusion decreased again.

For additional resource links, please visit our website at: www.genetics.emory.edu or call the Emory Lysosomal Storage Disease Center at 404-778-8565 or 1-800-200-1524

Can I move to a local hospital or home infusions for ERT?

If you are doing well with infusions and not having infusion related reactions, having infusions locally may be possible after your 10-12th infusion (~3-4 months). In order to switch you will need to work with your Genzyme treatment support representative, your insurance company, and Emory. Please note that this process may take weeks or months and it all depends on your insurance and how well you are doing with your infusions.

Where can I find more information on Fabry disease and enzyme replacement therapy?

Fabry Support & Information Group (FSIG)
108 NE 2nd Street, Suite C, P.O. Box 510, Concordia, MO 64020 Phone: (660) 463-1355
Internet: **http://www.fabry.org/**

The Fabry Community (Information about Fabry disease and ERT produced by Genzyme)
Internet: **http://www.fabrycommunity.com/**

Patient information on Fabry disease (a website sponsored by TKT)
Internet: **http://www.tktx.com/patient/fabry.htm**

References:

1. Desnick RJ, R Brady, J Barranger, AJ Collins, DP Germain, M Goldman, G Grabowski, S Packman, and WR Wilcox. Fabry Disease, an Under-Recognized Multisystemic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy. Ann Intern Med. 2003; 138:338-346.

2. Grinzaid, KA, E Geller, SL Hanna, and LJ Elsas. Cessation of Enzyme Replacement Therapy in Gaucher Disease. Genetics in Medicine. 2002: 4(6): 427-433.

3. Mignani, R., V. Panichi, A. Giudicissi, D. Taccola, F. Boscaro, C. Feletti, G. Moneti, and L. Cagnoli. Enzyme Replacement with agalsidase beta in kidney transplant patients with Fabry disease: A pilot study. Kidney International. 2004: 65:1381-1385.