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Protocol for Gaucher Disease Patients Started on Enzyme Replacement Therapy(ERT)

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Protocol for Gaucher disease patients started on ERT:

Background:

Definition: is the most common lysosomal storage disorder and represents a serious health concern for affected patients and their families. As a genetic disorder, Gaucher disease is an autosomal recessive lifelong condition with clinical heterogeneity as its hallmark. The disease frequently follows an unpredictable progressive course. Symptoms are usually multisystemic, often debilitating or disabling, and sometimes disfiguring, and they can lead to death.[1]

Causes: The disease is caused by a defect in the gene coding for the lysosomal enzyme beta-glucocerebrosidase (*GBA* gene); as a result, the cells of affected individuals are either unable to produce the enzyme or produce it in low amounts. This results in accumulation of glucocerebroside primarily in the spleen, liver, and bone marrow. The accumulation of glucocerebroside disturbs and inhibits the normal function of these organs and tissues and may lead to irreversible damage.[1]

Clinical features:

Gaucher disease (GD) can be classified into five types: three major clinical types (1, 2, and 3) and two other subtypes (perinatal-lethal and cardiovascular). Such classification is useful in determining prognosis and management.[2]

GD type 1 is characterized by the presence of bone disease (osteopenia, focal lytic or sclerotic lesions, and osteonecrosis) mimicking osteomyelitis, hepatosplenomegaly, anemia and thrombocytopenia, lung disease, without central nervous system manifestations. While neurological disease is essential inGD types 2 and 3; in the past, they were distinguished by age of onset and rate of disease progression, but these differences are not absolute. Disease with onset before age two years, limited psychomotor development, and a rapidly progressive course with death by age two to four years is classified as GD type 2. Patients with GD type 3 may have onset before age two years, but often have a more slowly progressive course, with survival into the third or fourth decade. The perinatal-lethal form is associated with ichthyosiform or collodion skin abnormalities or with nonimmune hydrops fetalis. The cardiovascular form is characterized by calcification of the aortic and mitral valves, mild splenomegaly, supranuclear ophthalmoplegia and corneal opacities. Cardiopulmonary complications have been described with all the clinical subtypes, although varying in frequency and severity.[2]

Diagnosis: is confirmed by deficiency of the enzyme on dry blood spot or white blood cell or cultured fibroblasts and DNA molecular testing of *GBA* gene.[1,2]

Treatment: includes :enzyme replacement therapy (ERT) or substrate reduction therapy (SRT), symptomatic based intervention which include: partial or total splenectomy for massive splenomegaly and thrombocytopenia. Supportive care for all patient may include: transfusion of blood products for severe anemia and bleeding, analgesics for bone pain, joint replacement surgery for relief from chronic pain and restoration of function, and oral bisphosphonates and calcium for osteoporosis.[1,2]

Purpose: The purpose of this policy is to dictate the management of patients with Gaucher disease who are eligible for enzyme replacement therapy.

Baseline assessments and investigations prior to initiation of enzyme replacement therapy(ERT)[3]:

- General examination: Height, Weight, Head circumference
- Vital signs: Blood pressure, Heart rate, respiratory rate and temprature
- Enzyme activity level
- DNA molecular testing for *GBA* gene
- CBC
- PT and PTT in patient with bleeding symptoms
- Chitotriosidase/CCL18/ TRAP/ACE levels
- Spleen and liver volume measurement by MRI

- MRI (sagittal T1-weighted scan of spine; T1-weighted scan of head of femur, DXA (spine and total body Z-scorec)
- Pain assessment
- Quality of life assessment
- ECG, chest X-ray, and Doppler echocardiogram (right ventricular systolic pressure) for patients aged >18 years

Enzyme replacement therapy(ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:

- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1mg/kg) IV; _____ (mg) IV.

Cerezyme® (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration.[4]

Preparation:

- Remove the required number of vials from refrigeration and allow to reach room temperature (approximately 20 – 30 minutes**(** Check the expiration date on the label and do not use past the expiration date
- Remove and dispose of plastic protective cap from each vial
- Prepare the vials for reconstitution using aseptic technique
- Reconstitute each 200 unit vial with 5.1 mL of Sterile Water for Injection, USP to yield a total volume of 5.3 mL per vial, 40 units/mL Reconstitute each 400 unit vial with 10.2 mL of Sterile Water for Injection, USP to yield a total volume of 10.6 mL per vial, 40 units/mL
- Direct the flow of the Sterile Water slowly to the inside wall of the vial
- To reduce the potential for stopper coring, insert the needle perpendicular to, and in the center of**,** the stopper and avoid multiple sticks through stoppers with the same needle**.**
- GENTLY SWIRL each vial, avoid excessive agitation, and set vials aside until completely dissolved
- Inspect each vial. The reconstituted solution should be clear. Do not use if foreign particles are present or if discolored**.**
- If foreign particles are observed or if the solution is discolored please report to Genzyme Medical Information
- Withdraw the required volume of reconstituted Cerezyme from each vial slowly
- Add the reconstituted solution slowly and directly into 0.9% Sodium Chloride, USP to yield a total volume between 100 mL and **200**mL
- Gently invert or massage the infusion bag to mix and do not shake the infusion bag
- The final solution should be clear and colorless but may contain a few thin translucent fibers
- An in-line low protein binding 0.2 µm filter can be used during administration (optional)
- Label the Cerezyme infusion per institutional[4]

The total volume of the administration should be delivered in approximately 1-2 hours.

Nurses: Monitor vital signs during (prior to each rate increase) and up to 1 hour following infusion. If abnormal, contact the physician to decrease the rate or temporarily hold the Cerezyme® infusion.

Undesirable effects: anaphylaxis and allergic reactions, infusion reactions, and immune mediated reactions, headache, nausea, vomiting, abdominal pain, fever, chills and fatigue.

Note:

- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Cerezyme® and initiate appropriate medical treatment.

- If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

Monitoring the response to enzyme replacement therapy[3]:

Assessment		Non symptomatic patients not receiving ERT		Patients receiving enzyme therapy not yet meeting therapeutic goals		Patients on enzyme therapy who are achieving therapeutic goals		At time of dose change or significant clinical complication
		Every 12 months	Every 24 months	Every 6 months	Every 12 months	Every 6-12 months	Every 12-24 months	
Physical examination including Height and weight		X		X		X		X
Hematology	CBC	X		X		X		X
	PT and PTT in patient with bleeding symptoms			X		X		
Biochemistry	Chitotriosidase /CCL18TRAP/ ACE	X		X		X		X
Visceral	Spleen volume and liver volume by MRI	X		X		X		
Skeletal	MRI (sagittal T1-weighted scan of spine; T1-weighted scan of head of femur)		X		X		X	
	DXA (spine and total body Z-scorec	X			X	X		
Pain		X		X		X		
Quality of life	SF-36d, PedsQL or KidscreenR	X		X		X		

References:

1. Grabowski GA. Gaucher disease: enzymology, genetics, and treatment. In: Harris H, Hirschhorn K, eds. Advances in Human Genetics. New York, NY: Plenum; 1993:377- 441.
2. Pastores GM, Hughes DA. Gaucher Disease. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. 2000 Jul 27 [updated 2015 Feb 26].
3. Kaplan P, Baris H, De Meirleir L, Di Rocco M, El-Beshlawy A, Huemer M, Martins AM, Nascu I, Rohrbach M, Steinbach L, Cohen IJ. Revised recommendations for the management of Gaucher disease in children. Eur J Pediatr. 2013 Apr;172(4):447-58
4. Cerezyme® product monograph. Cerezyme