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Preface

The Lysosomal Storage Disorders (LSD) are continuously expanding and reaching more than 50 diseases recently and they usually share the accumulation of waste products in the lysosomes, which may lead into formation of large intracellular vacuoles and cause multisystem disorders affecting vital organs in the body and contribute to high mortality and morbidity.

In the last decade, there was a huge advancement in the field of treatment of lysosomal storage disorders with the discovery of enzyme replacement therapy.

Enzyme replacement therapy (ERT) is a therapeutic approach where the specific enzyme that is absent or inactive in affected individuals is replaced with a functional enzyme molecule. Significant advances in enzyme replacement therapy have opened up a new era of hope for lysosomal storage disease (LSD) patients.

Currently, the ERT are available for several LSD including: Pompe disease, Gaucher disease, Fabry disease, Mucopolysaccharidosis type I, Mucopolysaccharidosis type II, Mucopolysaccharidosis type IV and Mucopolysaccharidosis type VI. Such field is continuously expanding and every year there is a new development of several medications.

Despite their discovery long time ago, the health care professional still faces challenges with resources to enough information regarding detailed administration of these medications.

This book is intended to summarize the dosages of ERT used in the treatment of LSD as supported by the best level of evidence that currently exists in the literature. This is accompanied by detailed protocol regarding their preparation, dosages, administration, storage, side effect and monitoring. To the best of our knowledge, this is the first review book that addresses this issue, and the authors hope that it will provide quick and easy access to a comprehensive list of medications used in this important clinical field.

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CONTENT

Protocol for Pompe Disease Patients Started on Myozyme®

Alglucosidase Alfa

1

Background:

Definition:
Pompe disease or Glycogen storage disease type II (GSD-II), is a rare autosomal recessive disease. It is one of lysosomal storage diseases.[1]

Causes:
It is caused by the deficiency of acid alpha-glucosidase (GAA), which is needed for the degradation of lysosomal glycogen.[1-4]

Classification:
It is classified into 3 major subtypes depending on the age of onset:
- Classic infantile
- Juvenile
- Adult

Clinical Features:
The classic infantile form usually presents within 1st month of life with hypotonia, and hypertrophic cardiomyopathy. Additional clinical features include: macroglossia, motor delay, high CK level, elevated liver enzymes and hepatomegaly. Patient may die from cardiopulmonary failure or aspiration pneumonia without reaching 1 year of age. The juvenile form is characterized by predominant skeletal muscle dysfunction with motor and respiratory problem but rarely cardiac involvement. Calf hypertrophy can be present mimicking Duchenne muscular dystrophy. Myopathy and respiratory insufficiency deteriorate gradually and patient become dependent on ventilator or wheelchair. The adult form develop in 3rd or 4th decade and affect the trunk and proximal limb muscle. Involvement of diaphragm is frequent and acute respiratory failure may be the initial symptom in some patients.[1-4]

Diagnosis:
The diagnosis is confirmed by deficiency of the enzyme on dried blood spot or white blood cell or fibroblasts or skeletal muscles and DNA molecular testing of GAA gene.

Treatment:
In 2006, enzyme replacement therapy (ERT) for Pompe disease (Myozyme®) was approved in the USA, Europe, and Canada, with subsequent approval in countries around the world.[1-4]

Baseline assessment and investigations[5,6]:

- Height, weight, head circumference
- Blood pressure, heart rate
- Cognitive and developmental assessment
- Motor assessment using Alberta Infant Motor Scale (AIMS), Peabody Developmental Motor Scale-2 (PDMS-2), Pediatric Evaluation of Disability Index (PEDI), and Pompe PEDI
- ECG and Echocardiogram
- ECG holter montoring
- Chest X-ray and spine X-ray
- Brain MRI (for infantile Pompe as leukodystrophy may occur)
- Pulmonary function test (only above 6 year of age)
- ENT evaluation (audiometry and ABR test)
- A videofluoroscopic swallowing assessment and gastroesophageal reflux evaluation
- CBC, diff
- Electrolytes
- Liver enzymes
- CPK level
- Bone profile and vitamin D levels
- Enzyme assay in dried blood spot or white blood cells.
- CRIM status determination in blood [collected by special tube from Genzyme company BD Vacutainer® CPT™ (Cell Preparation Tube) with Sodium Citrate, 4 mL should be extracted (Becton Dickinson), stored at room temperature (18-25ºC) and protected from light, CPT tube should be mixed by inversion 8-10 times after blood draw and centrifuged at 1800 xg for 30 minutes before shipping and the supernatant colour is a pale yellow].
- Anti-rhGAA Antibody Evaluation
- Skin fibroblasts for CRIM status
- DNA molecular testing for GAA to predict CRIM status.

Cross-reactive immunologic material (CRIM) status determination[7]:

CRIM status determination is an essential step prior to starting enzyme replacement therapy (Myozyme®). CRIM-negative patients who do not generate cross-reactive immunologic material generally develop high titer anti-rhGAA antibodies during ERT and require immunomodulation protocol (see page 17) early in the treatment course before the first dose. While CRIM-positive patients who

generate cross-reactive immunologic material respond to Myozyme® and do not need immunomodulation protocol. CRIM-negative status is common in Saudi population.

CRIM status can be determined by using either of the following:
- Acid alpha-glucosidase protein quantitation performed by an antibody-based method in cultured fibroblasts
- Molecular genetic testing to determine if the pathogenic variants reported to be CRIM-negative

Enzyme replacement therapy (ERT) administration protocol:

For immune modulation protocol see Figure 1.

Premedication (1 hour prior to ERT infusion) with:
- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1 mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1 mg/kg) IV; _____ (mg) IV.

Myozyme®: Alglucosidase alfa [8,9]

- **Dose:** 20 mg/kg (IV) every 2 weeks.

- **Strength:** 50mg (5mg/mL), single use vial.

Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 4 kg, give 100mg instead of 80mg.

- **Weight:** _____(kg): **calculated dose**_____(mg) IV.

- **Dilution:**
  - o For patients **<** 10 kg – dilute in 50 mL normal saline
  - o For patients **≥** 10 kg – dilute in 100 mL normal saline
  - o Range: 0.5 – 4 mg/mL (Total volume will depend on dilution chosen)

- **Dilution preferred**_____, **total volume** _____(mL).

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr,_____mL/hr.

The total volume of the administration should be delivered in approximately 3-4 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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions (during & up to 3 hours after infusion), risk of acute cardio-respiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions (during and up to 2 hours after infusion), and immune mediated reactions.

Note:
- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Myozyme® 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.

The definition of effective treatment is:
An improvement in or a prevention of progression of disease activity as indicated by stabilization in clinical condition associated with an improvement in the abnormalities present at baseline. This is defined as improved cardiac response by echocardiography and ventilator-free survival within 12 weeks of therapy.[5,6]

Discontinuation of treatment:
a) If the patient develops a life-threatening complication unlikely to benefit from further ERT. This includes severe infusion-related reactions that are not controlled with adequate and appropriate medication.

b) Failure to comply with recommended dose regimen or follow up clinic visits and/or investigations.

c) Non-responsiveness to ERT as assessed by echocardiography at 24 weeks after starting treatment.[5,6]

When to start Immune modulation therapy?

- CRIM-negative patients
- The team agreed to start immune modulation protocol for any patient diagnosed with Pompe disease as all documented cases in Saudi Arabia so far were CRIM-negative.

Table 1: Monitoring the response to enzyme replacement therapy [5,6]

Assessment	Frequency
General	
Height/length, weight, head circumference, blood pressure, heart rate	every visit
Cardiac Evaluation	
ECG and echocardiography	2, 8, and 12 and 24 weeks and then every 6-12 months
Holter monitoring	6 weeks, 12 weeks, 24 weeks, and then yearly
Respiratory Evaluation	
CXR	6 months and 12 months, then as clinically indicated
Pulmonary function tests	Every 6 months
ENT Evaluation	
Audiometry and (ABR) test	Every 12 months
Swallowing Assessment	
A videofluoroscopic evaluation, upper GI study and milk scan	As clinically indicated
Laboratory Tests	
CK, liver enzymes bone profile, CBC diff, electrolytes and vitamin D level	Every 3-6 months
Anti-GAA antibody titers	Every 3 months unless CRIM negative or if immunomodulatory therapy has been used
Cognitive and Developmental Assessments	
Denver Developmental screening test II, Bayley Scales of Infant and Toddler Development III	6 months, 12 months, then yearly
Motor Assessments	
Alberta Infant Motor Scale (AIMS), Peabody Developmental Motor Scale-2 (PDMS-2), Pediatric Evaluation of Disability Index (PEDI), and Pompe PEDI	Every 6 months

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Protocol for Immune Tolerance Induction for CRIM Negative Pompe Patients in the Naïve Setting

2

Timeline

• **Myozyme:**
Days 0, 14, 28, 42, 56, 70, 84, 98, 112, 126, 140
- Give every two weeks, unless clinical status and IARs require more administration (see Figure 1).

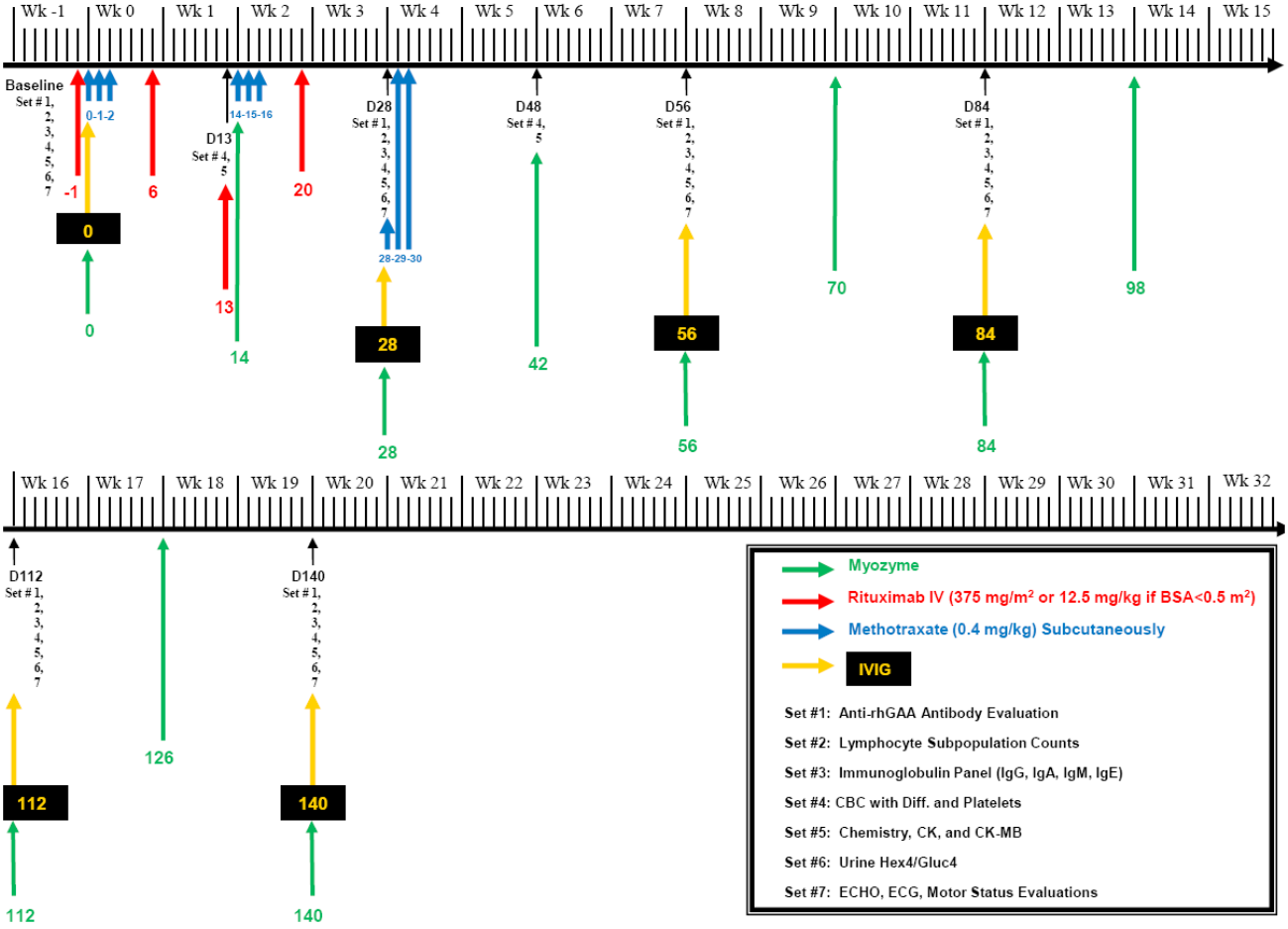
• **Rituximab:**
Days -1, 6, 13, 20
- Give four doses over 4 weeks.

• **Methotrexate:**
Days 0, 1,2,14,15,16, 28, 29, 30
- Give for three consecutive days (1 cycle) every 2 weeks for three cycles.
- Methotrexate needs to be administered 1 hour to Myozyme infusion on Day 0, 14 and 28.

• **IVIG*:**
Days 0, 28, 56, 84, 112, 140
- *Can be given more or less frequently depending upon immunoglobulin levels, CD19 levels, and clinical status.

• **Additional notes:**
- Changes may be made based on clinical status and antibody titers.
- IVIG can be delayed one day, if concerned with volume given in a single day. Also, IVIG can be given more often if indicated clinically.

Figure 1


Wk -1
Wk 0
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
Wk 6
Wk 7
Wk 8
Wk 9
Wk 10
Wk 11
Wk 12
Wk 13
Wk 14
Wk 15
Baseline
Set # 1, 2, 3, 4, 5, 6, 7
0-1-2
-1
0
6
D13
Set # 4, 5
14-15-16
13
14
20
D28
Set # 1, 2, 3, 4, 5, 6, 7
28-29-30
28
28
D48
Set # 4, 5
42
D56
Set # 1, 2, 3, 4, 5, 6, 7
56
56
70
D84
Set # 1, 2, 3, 4, 5, 6, 7
84
84
98
Wk 16
Wk 17
Wk 18
Wk 19
Wk 20
Wk 21
Wk 22
Wk 23
Wk 24
Wk 25
Wk 26
Wk 27
Wk 28
Wk 29
Wk 30
Wk 31
Wk 32
D112
Set # 1, 2, 3, 4, 5, 6, 7
112
112
126
D140
Set # 1, 2, 3, 4, 5, 6, 7
140
140
Myozyme
Rituximab IV (375 mg/m² or 12.5 mg/kg if BSA<0.5 m²)
Methotraxate (0.4 mg/kg) Subcutaneously
IVIG
Set #1: Anti-rhGAA Antibody Evaluation
Set #2: Lymphocyte Subpopulation Counts
Set #3: Immunoglobulin Panel (IgG, IgA, IgM, IgE)
Set #4: CBC with Diff. and Platelets
Set #5: Chemistry, CK, and CK-MB
Set #6: Urine Hex4/Gluc4
Set #7: ECHO, ECG, Motor Status Evaluations

Day (-1)

Baseline investigations: *(note: these lab results are important to monitor SE of your medications)*

- **Set 1:** Anti-rhGAA Antibody Evaluation
- **Set 2:** Lymphocyte Subpopulation Counts (CD3, CD4, CD8, CD19)
    - Monitor for vaccination (vaccinate only after CD19 recovery)
- **Set 3:** Immune Status/Immunoglobulin Panel (IgG, IgA, IgM, IgE)
    - Monitor for recovery status (when needed) with diphtheria and tetanus toxoid antibody titers
    - Monitor for IVIG administration
- **Set 4:** Hematology (CBC with differential, Platelets)
    - Monitor platelet counts for less than 50,000/mm^3
    - Monitor neutrophil counts for less than 500/mm^3
    - Monitor for infections resistant to treatment
- **Set 5:** Chemistry (ALT, AST, CK, CK-MB)
    - Monitor CK and CK-MB for increases greater than 2x baseline result
    - Monitor AST and ALT for increases greater than 3x baseline result
- **Set 6:** Urine Oligosaccharides (Hex4/Gluc4).

Day (-1):

Rituximab IV

- Dose: 375 mg/m^2/dose (IV);
  if BSA is less than 0.5 m^2, give 12.5 mg/kg (IV).
- Weight _____kg, height _____cm, BSA_____m^2.
- Calculated dose _____mg.
- Dilution Range: 1 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred _____, total volume _____mL.

- **Infusion Rate:**

1 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
2 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
3 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

- **Premedications may include:**
    - Acetaminophen (10-15 mg/kg) PO; _____ mg (PO).
    - Diphenhydramine (1 mg/kg) IV;_____mg (IV).
    - Methylprednisolone (1 mg/kg) IV; _____ mg (IV).
    - Granisetron (10 mcg/kg) IV;_____mcg (IV).

Side Effects:
Infusion related reactions (i.e. hives, itching, swelling of lips, tongue, throat or face, sudden cough, difficulty breathing, weakness, dizziness, palpitations and chest pain), chills, infections, body aches, tiredness, and low white blood cells.

Nursing:
• Monitor vital signs Q _____ min.
• Call MD if any side effect develops.

Day (0): Methotrexate, Myozyme®, IVIG

(a) Methotrexate: (dose 1 of cycle 1)
To be given 1 hour prior to Myozyme®.
Given in cycles; each cycle is 3 consecutive days.

• Dose: 0.4 mg/kg Subcut or PO once.
• Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
• Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
• Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

(b) Myozyme®: Alglucosidase alfa.
• Dose: 20 mg/kg (IV).
• Weight: _____kg: calculated dose _____mg (IV).
• Dilution Range: 0.5 - 4mg/mL.
(Total volume will depend on dilution chosen)
• Dilution preferred_____, total volume _____mL.

Special Precautions:
• Stable only in Normal Saline.
• The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

(c) IVIG:
- Dose: 400 - 500 mg/kg.
- Weight: _____ kg, calculated dose: _____mg.
- Please follow the nursing instructions and the infusion rate as per the "IVIG protocol for Pediatrics" - Appendix I.

Day (1): Methotrexate

Methotrexate: (dose 2 of cycle 1)
- Dose: 0.4 mg/kg Subcut or PO once.
- Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
- Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
- Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

Day (2): Methotrexate

Methotrexate: (dose 3 of cycle 1)
• Dose: 0.4 mg/kg Subcut or PO once.
• Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
• Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
• Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

Day (6):

Rituximab IV
• Dose: 375 mg/m^2/dose (IV);
if BSA is less than 0.5 m^2, give 12.5 mg/kg (IV).
• Weight _____kg, height _____cm, BSA_____m^2.
• Calculated dose _____mg.
• Dilution Range: 1 - 4 mg/mL.
(Total volume will depend on dilution chosen)
• Dilution preferred _____, total volume _____mL.

• **Infusion Rate:**
1 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
2 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
3 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

• **Premedications may include:**
- Acetaminophen (10-15 mg/kg) PO; _____ mg (PO).
- Diphenhydramine (1 mg/kg) IV;_____mg (IV).
- Methylprednisolone (1 mg/kg) IV; _____ mg (IV).
- Granisetron (10 mcg/kg) IV;_____mcg (IV).

Side Effects:
Infusion related reactions (i.e. hives, itching, swelling of lips, tongue, throat or face, sudden cough, difficulty breathing, weakness, dizziness, palpitations and chest pain), chills, infections, body aches, tiredness, and low white blood cells.

Nursing:
- Monitor vital signs Q _____ min.
- Call MD if any side effect develops.

Day (13):

Repeat investigations: *(note: these lab results are important to monitor SE of your medications)*
- ***Set 4:*** Hematology (CBC with differential, Platelets)
  - Monitor platelet counts for less than 50,000/mm^3
  - Monitor neutrophil counts for less than 500/mm^3
  - Monitor for infections resistant to treatment

- ***Set 5:*** Chemistry (ALT, AST, CK, CK-MB)
  - Monitor CK and CK-MB for increases greater than 2x baseline result
  - Monitor AST and ALT for increases greater than 3x baseline result

Day (13):

Rituximab IV
- Dose: 375 mg/m^2/dose (IV);
  if BSA is less than 0.5 m^2, give 12.5 mg/kg (IV).
- Weight _____kg, height _____cm, BSA_____m^2.
- Calculated dose _____mg.
- Dilution Range: 1 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred _____, total volume _____mL.

- **Infusion Rate:**

1 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
2 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
3 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

- **Premedications may include:**
    - Acetaminophen (10-15 mg/kg) PO; _____ mg (PO).
    - Diphenhydramine (1 mg/kg) IV;_____mg (IV).
    - Methylprednisolone (1 mg/kg) IV; _____ mg (IV).
    - Granisetron (10 mcg/kg) IV;_____mcg (IV).

Side Effects:
Infusion related reactions (i.e. hives, itching, swelling of lips, tongue, throat or face, sudden cough, difficulty breathing, weakness, dizziness, palpitations and chest pain), chills, infections, body aches, tiredness, and low white blood cells.

Nursing:
- Monitor vital signs Q _____ min.
- Call MD if any side effect develops.

Day (14): Methotrexate, Myozyme®

(a) Methotrexate: (dose 1 of cycle 2)
To be given 1 hour prior to Myozyme®.
Given in cycles; each cycle is 3 consecutive days.

- Dose: 0.4 mg/kg Subcut or PO once.
- Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
- Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
- Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

(b) Myozyme®: Alglucosidase alfa
- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

Day (15): Methotrexate

Methotrexate: (dose 2 of cycle 1)
- Dose: 0.4 mg/kg Subcut or PO once.
- Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
- Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
- Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

Day (16): Methotrexate

Methotrexate: (dose 3 of cycle 1)
• Dose: 0.4 mg/kg Subcut or PO once.
• Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
• Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
• Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

Day (20):

Rituximab IV
• Dose: 375 mg/m^2/dose (IV);
if BSA is less than 0.5 m^2, give 12.5 mg/kg (IV).
• Weight _____kg, height _____cm, BSA_____m^2.
• Calculated dose _____mg.
• Dilution Range: 1 - 4 mg/mL.
(Total volume will depend on dilution chosen)
• Dilution preferred _____, total volume _____mL.

• **Infusion Rate:**
1 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
2 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
3 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

• **Premedications may include:**
  • Acetaminophen (10-15 mg/kg) PO; _____ mg (PO).
  • Diphenhydramine (1 mg/kg) IV;_____mg (IV).
  • Methylprednisolone (1 mg/kg) IV; _____ mg (IV).
  • Granisetron (10 mcg/kg) IV;_____mcg (IV).

Side Effects:
Infusion related reactions (i.e. hives, itching, swelling of lips, tongue, throat or face, sudden cough, difficulty breathing, weakness, dizziness, palpitations and chest pain), chills, infections, body aches, tiredness, and low white blood cells.

Nursing:
- Monitor vital signs Q _____ min.
- Call MD if any side effect develops.

Day (28)

Repeat investigations: *(note: these lab results are important to monitor SE of your medications)*
- **Set 1:** Anti-rhGAA Antibody Evaluation
- **Set 2:** Lymphocyte Subpopulation Counts (CD3, CD4, CD8, CD19)
    - Monitor for vaccination (vaccinate only after CD19 recovery)
- **Set 3:** Immune Status/Immunoglobulin Panel (IgG, IgA, IgM, IgE)
    - Monitor for recovery status (when needed) with diphtheria and tetanus toxoid antibody titers
    - Monitor for IVIG administration
- **Set 4*:*** Hematology (CBC with differential, Platelets)
    - Monitor platelet counts for less than 50,000/mm^3
    - Monitor neutrophil counts for less than 500/mm^3
    - Monitor for infections resistant to treatment
- **Set 5:** Chemistry (ALT, AST, CK, CK-MB)
    - Monitor CK and CK-MB for increases greater than 2x baseline result
    - Monitor AST and ALT for increases greater than 3x baseline result
- **Set 6:** Urine Oligosaccharides (Hex4/Gluc4).

Day (28): Methotrexate, Myozyme®, IVIG

(a) Methotrexate: (dose 1 of cycle 1)
To be given 1 hour prior to Myozyme®.
Given in cycles; each cycle is 3 consecutive days.

- Dose: 0.4 mg/kg Subcut or PO once.
- Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
• Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
• Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

(b) Myozyme®: Alglucosidase alfa
• Dose: 20 mg/kg (IV).
• Weight: _____kg: calculated dose _____mg (IV).
• Dilution Range: 0.5 - 4 mg/mL.
(Total volume will depend on dilution chosen)
• Dilution preferred_____, total volume _____mL.

Special Precautions:
• Stable only in Normal Saline.
• The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
• 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
• 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
• 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
• 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

(c) IVIG:
• Dose: 400 - 500 mg/kg.
• Weight: _____ kg, calculated dose: _____mg.
• Please follow the nursing instructions and the infusion rate as per the "IVIG protocol for Pediatrics" - Appendix I.

Day (29): Methotrexate

Methotrexate: (dose 2 of cycle 3)
• Dose: 0.4 mg/kg Subcut or PO once.
• Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
• Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
• Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

Day (30): Methotrexate

Methotrexate: (dose 3 of cycle 3)
• Dose: 0.4 mg/kg Subcut or PO once.
• Weight _____kg; calculated dose: _____mg; route_____.

Premedications may include:
• Acetaminophen (10-15 mg/kg) PO;_____ mg (PO).
• Granisetron (10 mcg/kg) IV; _____mcg (IV).

Side Effects:
Ulcerative stomatitis, leukopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

HOLD dose for ANC less than 750 (OR) liver function tests (LFTs) greater than 5x normal.

Day (42):

Repeat investigations: *(note: these lab results are important to monitor SE of your medications)*

- ***Set 4:*** Hematology (CBC with differential, Platelets)
  - Monitor platelet counts for less than 50,000/mm^3
  - Monitor neutrophil counts for less than 500/mm^3
  - Monitor for infections resistant to treatment

- ***Set 5:*** Chemistry (ALT, AST, CK, CK-MB)
  - Monitor CK and CK-MB for increases greater than 2x baseline result
  - Monitor AST and ALT for increases greater than 3x baseline result

Day (42):

Myozyme®: Alglucosidase alfa

- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:

- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:

- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

Day (56)

Repeat investigations: *(note: these lab results are important to monitor SE of your medications)*

- **Set 1:** Anti-rhGAA Antibody Evaluation
- **Set 2:** Lymphocyte Subpopulation Counts (CD3, CD4, CD8, CD19)
  - Monitor for vaccination (vaccinate only after CD19 recovery)
- **Set 3:** Immune Status/Immunoglobulin Panel (IgG, IgA, IgM, IgE)
  - Monitor for recovery status (when needed) with diphtheria and tetanus toxoid antibody titers
  - Monitor for IVIG administration
- **Set 4:** Hematology (CBC with differential, Platelets)
  - Monitor platelet counts for less than 50,000/mm^3
  - Monitor neutrophil counts for less than 500/mm^3
  - Monitor for infections resistant to treatment
- **Set 5:** Chemistry (ALT, AST, CK, CK-MB)
  - Monitor CK and CK-MB for increases greater than 2x baseline result
  - Monitor AST and ALT for increases greater than 3x baseline result
- **Set 6:** Urine Oligosaccharides (Hex4/Gluc4).

Day (56): Myozyme®, IVIG

(a) Myozyme®: Alglucosidase alfa
- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

(b) IVIG:
- Dose: 400 - 500 mg/kg.
- Weight: _____ kg, calculated dose: _____mg.
- Please follow the nursing instructions and the infusion rate as per the "IVIG protocol for Pediatrics" - Appendix I.

Day (70): Myozyme®

Myozyme®: Alglucosidase alfa
- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

Day (84):
Repeat investigations: *(note: these lab results are important to monitor SE of your medications)*

- **Set 1:** Anti-rhGAA Antibody Evaluation
- **Set 2:** Lymphocyte Subpopulation Counts (CD3, CD4, CD8, CD19)
  - Monitor for vaccination (vaccinate only after CD19 recovery)
- **Set 3:** Immune Status/Immunoglobulin Panel (IgG, IgA, IgM, IgE)
  - Monitor for recovery status (when needed) with diphtheria and tetanus toxoid antibody titers
  - Monitor for IVIG administration
- **Set 4*:*** Hematology (CBC with differential, Platelets)
  - Monitor platelet counts for less than 50,000/mm^3
  - Monitor neutrophil counts for less than 500/mm^3
  - Monitor for infections resistant to treatment
- **Set 5:** Chemistry (ALT, AST, CK, CK-MB)
  - Monitor CK and CK-MB for increases greater than 2x baseline result
  - Monitor AST and ALT for increases greater than 3x baseline result
- **Set 6:** Urine Oligosaccharides (Hex4/Gluc4).

Day (84): Myozyme®, IVIG

(a) Myozyme®: Alglucosidase alfa

- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

(b) IVIG:
- Dose: 400 - 500 mg/kg.
- Weight: _____ kg, calculated dose: _____mg.
- Please follow the nursing instructions and the infusion rate as per the "IVIG protocol for Pediatrics" - Appendix I.

Day (98): Myozyme®

Myozyme®: Alglucosidase alfa
- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

Day (112):
- **Set 1:** Anti-rhGAA Antibody Evaluation
- **Set 2:** Lymphocyte Subpopulation Counts (CD3, CD4, CD8, CD19)
    - Monitor for vaccination (vaccinate only after CD19 recovery)
- **Set 3:** Immune Status/Immunoglobulin Panel (IgG, IgA, IgM, IgE)
    - Monitor for recovery status (when needed) with diphtheria and tetanus toxoid antibody titers
    - Monitor for IVIG administration
- **Set 4:** Hematology (CBC with differential, Platelets)
    - Monitor platelet counts for less than 50,000/mm^3
    - Monitor neutrophil counts for less than 500/mm^3
    - Monitor for infections resistant to treatment
- **Set 5:** Chemistry (ALT, AST, CK, CK-MB)
    - Monitor CK and CK-MB for increases greater than 2x baseline result
    - Monitor AST and ALT for increases greater than 3x baseline result
- **Set 6:** Urine Oligosaccharides (Hex4/Gluc4).

Day (112): Myozyme®, IVIG

(a) Myozyme®: Alglucosidase alfa
- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

(b) IVIG:
- Dose: 400 - 500 mg/kg.
- Weight: _____ kg, calculated dose: _____mg.
- Please follow the nursing instructions and the infusion rate as per the "IVIG protocol for Pediatrics" - Appendix I.

Day (126): Myozyme®

Myozyme®: Alglucosidase alfa
- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:
Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

Day (140):

Repeat investigations: *(note: these lab results are important to monitor SE of your medications)*
- **Set 1:** Anti-rhGAA Antibody Evaluation
- **Set 2:** Lymphocyte Subpopulation Counts (CD3, CD4, CD8, CD19)
    - Monitor for vaccination (vaccinate only after CD19 recovery)
- **Set 3:** Immune Status/Immunoglobulin Panel (IgG, IgA, IgM, IgE)
    - Monitor for recovery status (when needed) with diphtheria and tetanus toxoid antibody titers
    - Monitor for IVIG administration
- **Set 4:** Hematology (CBC with differential, Platelets)
    - Monitor platelet counts for less than 50,000/mm^3
    - Monitor neutrophil counts for less than 500/mm^3
    - Monitor for infections resistant to treatment
- **Set 5:** Chemistry (ALT, AST, CK, CK-MB)
    - Monitor CK and CK-MB for increases greater than 2x baseline result
    - Monitor AST and ALT for increases greater than 3x baseline result
- **Set 6:** Urine Oligosaccharides (Hex4/Gluc4).

(a) Myozyme®: Alglucosidase alfa

- Dose: 20 mg/kg (IV).
- Weight: _____kg: calculated dose _____mg (IV).
- Dilution Range: 0.5 - 4 mg/mL.
  (Total volume will depend on dilution chosen)
- Dilution preferred_____, total volume _____mL.

Special Precautions:

- Stable only in Normal Saline.
- The diluted Myozyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:

- 1 mg/kg/hr x 30 min; _____mg/hr,_____mL/hr.
- 3 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 5 mg/kg/hr x 30 min; _____mg/hr, _____mL/hr.
- 7 mg/kg/hr until complete; _____mg/hr, _____mL/hr.

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 Myozyme® infusion.

Side Effects:

Anaphylaxis and allergic reactions, risk of acute cardiorespiratory failure, risk of cardiac arrhythmia and sudden cardiac death during general anesthesia for central venous catheter placement, infusion reactions, and immune mediated reactions.

(b) IVIG:

- Dose: 400 - 500 mg/kg.
- Weight: _____ kg, calculated dose: _____mg.
- Please follow the nursing instructions and the infusion rate as per the "IVIG protocol for Pediatrics" - Appendix I.

Appendix I

INTRAVENOUS IMMUNE GLOBULIN 5% (HUMAN)

Pediatric Protocol (Order Form)

(Please check one)

IMMUNOLOGY: **HYPOGAMMAGLOBULINEMIA** ☐ **GUILLAIN BARRE SYNDROME** ☐

HAEMATOLOGY: **BONE MARROW TRANSPLANT** ☐

IMMUNE THROMBOCYTOPENIC PURPURA (ITP) ☐

INFECTIOUS DISEASE ☐ **VIRAL MYOCARDITIS** ☐ **KAWASAKI DISEASE** ☐

SEVERE ABO OR RH INCOMPATIBILITY ☐

LABORATORY **Pre-infusion blood work: CROSS OUT ORDERS TO BE OMITTED**

IMMUNOLOGY: ☐ CBC with differential, ESR, liver function enzymes, quantitative immunoglobulins

HAEMATOLOGY: ☐ ITP: CBC with differential, quantitative immunoglobulins, direct antiglobulin test, Epstein-Barr Virus (EBV) serology, anti-Nuclear-Antibody (ANA), anti-double stranded Deoxyribonucleic acid (DNA)

INFECTIOUS DISEASE: ☐ CBC with differential

NEONATAL USE: ☐ CBC with reticulocyte, Coombs test, Serum bilirubin

OTHER TESTS: _____

NURSING

1. Record baseline height & weight
2. Record heart rate (HR), respiratory rate (RR), temperature (T) and blood pressure (BP) immediately before infusion and 15, 30 & 60 minutes after starting infusion; then hourly until 30 minutes after the infusion has ended.
3. Have Anaphylaxis Kit at beside. If unavailable, please obtain from the Pharmacy.
4. Have Paediatric emergency drug print-out on bed in patient's room.
5. Diet as tolerated, activity as tolerated.
6. Notify MD if HR 30 beats/min greater than baseline:
   and/or RR 10/min greater than baseline
   and/or T 1.5°C greater than baseline, if baseline greater than 38.5°C
   and/or T 1°C greater than baseline, if baseline greater than 38.5°C
   and/or systolic BP greater or equal to 15 mmHg above baseline
   and/or diastolic BP greater or equal to 15 mmHg above baseline
   and/or wheezing, chills, rash, urticaria, itching, flushing, myalgias or
   Central nervous system (CNS) / behavior change is observed

INFUSION

1. Start IV normal saline _____ ml/hr
2. Pre-medicate patients with a history of allergic reactions with Hydrocortisone _____ mg IV (*50mg if less than 30 kg, 100 mg if 30 kg or greater*) 15 minutes prior to immune globulin infusion. (NOTE: Not given to neonates or bone marrow transplant patients).
3. Intravenous Immunoglobulin, Human _____Gm IV (____Gm/kg/dose) as a single daily dose for___ day (s).

   Infuse at: _____ ml/hr x 15 min (0.6 ml/kg/hr; maximum 15 ml/hr)
   _____ ml/hr x 15 min (1.2 ml/kg/hr; maximum 24 ml/hr)
   _____ ml/hr x 15 min (2.4 ml/kg/hr; maximum 42 ml/hr)
   _____ ml/hr x 15 min till finished (4.8 ml/kg/hr; maximum 90 ml/hr)

Adapted from the "Parental Therapy Manual" © 2011 - PHARMACEUTICAL CARE SERVICES at NATIONAL GUARD HEALTH AFFAIRS; Riyadh, KSA.

Note: Other hospitals' specific Pediatric IVIG Protocols can be used if available.

References

1. Messinger YH, Mendelsohn NJ, Rhead W, et al. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. Genetics in medicine : official journal of the American College of Medical Genetics. 2012;14(1):135-142. doi:10.1038/gim.2011.4

Protocol for Mucopolysaccharidosis type I (MPS I) Patients Started on Aldurazyme® (Laronidase)

3

Background:

Definition:
Mucopolysaccharidosis type I (MPS I) is a rare, life-threatening autosomal recessive lysosomal storage disease with pathologic manifestations in most organ systems and tissues.

Causes:
The disease is caused by a defect in the gene coding for the lysosomal enzyme alpha-L-iduronidase (IDUA); as a result, the cells of affected individuals are either unable to produce the enzyme or produce it in low amounts. This results in an inability of the lysosome to effect the stepwise degradation of the glycosaminoglycans (GAGs), dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. Because the disease is rare, and early symptoms can mimic other more common disorders, MPS I is often underrecognized and diagnostic delays are common.[1]

Classification:
- MPS I H (Hurler) syndrome
- MPS I H/S (Hurler-Scheie)
- MPS I S (Scheie) syndrome

All types share the same gene defect and biochemical abnormalities and are differentiated phenotypically: Hurler syndrome represents the most severe phenotype with earlier age of onset while Scheie syndrome represent later age of onset and mildest phenotype and Hurler-Scheie in between the 2 spectrum.

Clinical features:
The most severely affected patients at one end of the MPS I continuum are categorized as having the "Hurler" phenotype. These patients experience rapidly progressive disease manifestations beginning in infancy and are diagnosed at a median age of 0.8 years.[2] Earliest symptoms include development of "coarse" facial features, corneal clouding, hepatomegaly, kyphosis, and inguinal and umbilical hernias. Later symptoms include dysostosis multiplex; severe arthropathy; impaired hearing, respiration, and cardiac function, and progressive mental impairment. Without treatment, approximately 75% of patients with Hurler syndrome die before age of 10; usually from obstructive airway disease, respiratory infections, and cardiac complications. Scheie syndrome represents later age of onset and mildest phenotype and Hurler-Scheie is in between the 2 spectrums.[1-3]

Diagnosis:
Usually by findings of high dermatan and heparan sulfates in urine mucopolysaccharide analysis. The diagnosis is confirmed by deficiency of the enzyme on dried blood spot or white blood cell and DNA molecular testing of IDUA gene.[2]

Treatment:
Includes symptom-based interventions, enzyme replacement therapy with Aldurazyme® (laronidase) and hematopoietic stem cell transplantation (particularly very young, severely affected patients).[1-5]

Baseline assessments and investigations prior to initiation of enzyme replacement therapy (ERT)[6,7]:

- Height, weight, head circumference
- Blood pressure
- Enzyme activity level
- DNA molecular testing for IDUA gene
- IgG antibody test
- CBC, diff
- Chemistry (electrolytes, BUN, serum creatinine)
- Liver enzymes
- CPK level
- Bone profile and vitamin D levels
- Urine for mucopolysaccharides
- Urine analysis
- Neurology evaluation
- MRI of brain and spine
- Median nerve conduction velocity
- Cognitive testing [developmental quotient (DQ) or intelligence quotient (IQ)]
- ENT evaluation (audiometry and ABR test)
- Ophthalmology evaluation (visual acuity, retinal examination, corneal examination)
- Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)
- Cardiology evaluation (ECG, Echocardiogram)
- Skeletal survey
- Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound.
- Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.

Enzyme replacement therapy (ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:
- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1 mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1 mg/kg) IV; _____ (mg) IV.

Aldurazyme® (Laronidase)[8-15]

- **Dose:** 0.58 mg/kg (100unit/kg) IV once weekly.

- **Strength:** 5mL (2.9 mg/5mL) = 500 units/5mL, single use vial.

Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 4 kg give, 2.9mg (500unit) instead of 2.32mg (400unit).

- **Weight:** _____(kg): **calculated dose**_____(mg) IV.

- **Dilution:**

o For patients **≤** 20 kg – dilute in 100 mL normal saline
o For patients up to 30 kg with underlying cardiac or respiratory compromise – dilute in 100 mL normal saline.
o For patients **>** 20 kg – dilute in 250 mL normal saline

Special Precautions:
- Stable only in Normal Saline.
- The diluted Aldurazyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:[14,15]
- The initial infusion rate of 2 U/kg/h may be incrementally increased every fifteen minutes, if tolerated, to a maximum of 43 U/kg/h. Therefore, you could apply the following regimens:

• For weights less than or equal to 20 kg:

Infusion rate	When to increase infusion rate to the next level
2 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
4 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
8 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
16 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
32 mL/hour for (~3 hours)	for remainder of infusion

The total volume of the administration should be delivered in approximately 3-4 hours.

• For weights more than 20 kg:

Infusion rate	When to increase infusion rate to the next level
5 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
10 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
20 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
40 mL/hour for 15 minutes	If stable vital signs, increase the rate to ...
80 mL/hour for (~3 hours)	for remainder of infusion

The total volume of the administration should be delivered in approximately 3-4 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 Aldurazyme® infusion.

Side Effects:
The most commonly reported infusion reactions were pyrexia, chills, blood pressure increased, tachycardia, and oxygen saturation decreased. The most frequently occurring adverse reactions are rash, upper respiratory tract infection, injection site reaction, hyperreflexia, paresthesia, flushing, and poor venous access.
Less common but serious side effects: anaphylaxis and allergic reactions (during & up to 3 hours after infusion), risk of acute cardio-respiratory failure.

Note:
- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Aldurazyme® 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

Table 2: Monitoring the response to enzyme replacement therapy [6,7]

	Every 6 months	Every 12 months	Every Other Year
General Evaluation			
Medical history Physical examination General appearance	X		
Lab Tests			
CBC, diff Electrolytes Liver enzymes CPK level Bone profile & vitamin D levels	X		

	Every 6 months	Every 12 months	Every Other Year
Neurology			
MRI of brain & spine			X
Median nerve conduction velocity			X
Cognitive testing (developmental quotient (DQ) or intelligence quotient (IQ)		X	
ENT Evaluation			
Audiometry and ABR test		X	
Ophthalmology Evaluation			
Visual acuity, retinal examination, corneal examination		X	
Respiratory Evaluation			
Chest X-ray, forced vital capacity, forced expiratory volume, sleep study		X	
Cardiology Evaluation			
ECG, Echocardiogram			X

	Every 6 months	Every 12 months	Every Other Year
Others			
Skeletal survey			X
Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound			X
Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life		X	

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Protocol for Mucopolysaccharidosis type II (MPS II) Patients Started on Elaprase®

(Idursulfase)

4

Background:

Definition:
Mucopolysaccharidosis type II (MPS II) also known as Hunter syndrome is a rare, life-threatening X-linked lysosomal storage disease with pathologic manifestations in most organ systems and tissues.

Causes:
The disease is caused by a defect in the gene coding for the lysosomal enzyme iduronate 2-sulfatase (I2S) (IDS 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 an inability of the lysosome to effect the stepwise degradation of the glycosaminoglycans (GAGs), dermatan sulfate and heparan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. Because the disease is rare, and early symptoms can mimic other more common disorders, MPS II is often under recognized and diagnostic delays are common.[1]

Clinical features:
The majority of patients are males; on rare instance heterozygous females manifest findings. Age of onset, disease severity, and rate of progression vary significantly among affected males. In those with early progressive disease, CNS involvement (manifest primarily by progressive cognitive deterioration), progressive airway disease, and cardiac disease usually result in death in the first or second decade of life. In those with slowly progressive disease, the CNS is not (or is minimally) affected, although the effect of GAG accumulation on other organ systems may be early progressive to the same degree as in those who have progressive cognitive decline. Survival into the early adult years with normal intelligence is common in the slowly progressing form of the disease. Additional findings in both forms of MPS II include: short stature; macrocephaly with or without communicating hydrocephalus; macroglossia; hoarse voice; conductive and sensorineural hearing loss; hepato-splenomegaly; dysostosis multiplex; spinal stenosis; and carpal tunnel syndrome.[1,2,3]

Diagnosis:
Usually by findings of high dermatan and heparan sulfates in urine mucopolysaccharide analysis. The diagnosis is confirmed by deficiency of the enzyme on dried blood spot or white blood cell and DNA molecular testing of IDS gene.

Treatment:
Includes symptom-based interventions, enzyme replacement therapy with Elaprase® (idursulfase).[1,2,3]

Baseline assessments and investigations prior to initiation of enzyme replacement therapy (ERT)[3,6-8]:

- Height, weight, head circumference
- Blood pressure
- Enzyme activity level
- DNA molecular testing for IDS gene
- IgG antibody test
- CBC, diff
- Chemistry (electrolytes, BUN, serum creatinine)
- Liver enzymes
- CPK level
- Bone profile and vitamin D levels
- Urine for mucopolysaccharides
- Urine analysis
- Neurology evaluation
- MRI of brain and spine
- Median nerve conduction velocity
- Cognitive testing [developmental quotient (DQ) or intelligence quotient (IQ)]
- ENT evaluation (audiometry and ABR test)
- Ophthalmology evaluation (visual acuity, retinal examination, corneal examination)
- Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)
- Cardiology evaluation (ECG, Echocardiogram)
- Skeletal survey
- Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound.
- Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.
- 12-minute walking test (12MWT) and 3-minute stair climb (3MSC)

Enzyme replacement therapy (ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:
- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1 mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1 mg/kg) IV; _____ (mg) IV.

Elaprase® (Idursulfase) [4,5]

- **Dose:** 0.5 mg/kg (IV) once weekly.

- **Strength:** 3mL (6 mg/3mL), single use vial.
  Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 10 kg, give 6mg instead of 5mg.

- **Weight:** _____(kg): **calculated dose**_____(mg) IV.

- **Dilution:**
  o Dilute in 100 mL normal saline

Special Precautions:
- Stable ONLY in Normal Saline.
- The diluted Elaprase® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate:
- Initial rate of 8 mL/hour for the first 15 minutes. If tolerated, may increase rate by 8 mL/hour increments every 15 minutes; maximum infusion rate up to 100 mL/hour.
- Rate may be decreased, temporarily stopped, or discontinued based on tolerance.
- Initial infusion should be over 3 hours; if tolerated, subsequent infusions may be gradually reduced to a 1-hour infusion. Total infusion time should not exceed 8 hours.[5]

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 Elaprase® infusion.

Side Effects:
Most common are infusion-related reactions; headache, hypertension, flushing, nausea, vomiting, diarrhea, abdominal pain, dyspepsia, infusion site reactions, wheezing, dyspnea, urticaria, rash, pruritus.

Note:
- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Elaprase® 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.

Table 3: Monitoring the response to enzyme replacement therapy[3, 6-8]

	Every 6 months	Every 12 months	Every Other Year
General			
Medical history Physical examination General appearance	x		
Lab Tests			
CBC, diff Electrolytes Liver enzymes CPK level Bone profile and vitamin D levels	x		
IgG antibody test		x	

	Every 6 months	Every 12 months	Every Other Year
Neurology			
MRI of brain and spine			x
Median nerve conduction velocity			x
Cognitive Testing (developmental quotient (DQ) or intelligence quotient (IQ)		x	
ENT Evaluation			
Audiometry and ABR test		x	
Ophthalmology Evaluation			
Visual acuity, retinal examination, corneal examination		x	
Respiratory Evaluation			
Chest X-ray, forced vital capacity, forced expiratory volume, sleep study		x	
Cardiology Evaluation			
ECG, Echocardiogram			x

	Every 6 months	Every 12 months	Every Other Year
Others			
Skeletal survey			x
Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound.			x
Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.		x	
12-minute walking test (12MWT) and 3-minute stair climb (3MSC)		x	

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Protocol for Mucopolysaccharidosis type IVA (MPS IVA) Patients Started on VIMIZIM®

(Elosulfase Alfa)

5

Background:

Definition:
Mucopolysaccharidosis type IVA (MPS IVA) or Morquio A Syndrome is a rare, autosomal recessive lysosomal storage disease associated with skeletal and joint abnormalities and significant non-skeletal manifestations including respiratory disease, spinal cord compression, cardiac disease, impaired vision, hearing loss, and dental problems.[1-4]

Causes:
It is caused by deficiency of the enzyme N-acetylgalactosamine-6-sulfatase (GALNS) due to a mutation in GALNS gene.[1-4]

Clinical features:
The phenotype is heterogeneous and ranges from a severe and rapidly progressive early-onset form to a slowly progressive later-onset form. Patients have no unique clinical findings at birth. The severe form is usually apparent between ages 1-3 years. Initial manifestations mainly skeletal abnormalities including: kyphoscoliosis, knock-knee (genu valgum), and pectus carinatum. The slowly progressive form may not become evident until late childhood or adolescence often first manifesting as hip problems (pain, stiffness, and Legg Perthes disease). Progressive bone and joint involvement leads to short stature, and pain and arthritis that become disabling. Involvement of other organ systems can lead to significant morbidity, including respiratory compromise, obstructive sleep apnea, valvular heart disease, hearing impairment, visual impairment from corneal clouding, dental abnormalities, and hepatomegaly. Compression of the spinal cord is a common complication that results in neurologic injury. Children with MPS IVA have normal intellectual abilities at the onset of the disease.[1-4]

Diagnosis:
Usually by findings of high keratan sulfate in urine mucopolysaccharide analysis. The diagnosis is confirmed by deficiency of the enzyme on dried blood spot or white blood cell and DNA molecular testing of GALNS gene. [1-4]

Treatment:
Includes symptom-based interventions, enzyme replacement therapy with VIMIZIM® (elosulfase alfa). [1-4]

Baseline assessments and investigations prior to initiation of enzyme replacement therapy (ERT):[4]

- General examination: Height, weight, head circumference
- Vital signs: Blood pressure, Heart rate, respiratory rate and temprature
- Enzyme activity level
- DNA molecular testing for GALNS gene
- IgG antibody test
- CBC, diff
- Chemistry (electrolytes, BUN, serum creatinine)
- Liver enzymes
- CPK level
- Bone profile and vitamin D levels
- Urine for mucopolysaccharides
- Urine analysis
- Standardized upper extremity function test (eg. Mallet test see Appendix II)
- Endurance measured by Timed 25-Foot Walking (T25W) or 6-minute walking test (This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes).
- Neurology evaluation
- MRI of brain and spine
- Median nerve conduction velocity
- Cognitive testing [developmental quotient (DQ) or intelligence quotient (IQ)]
- ENT evaluation (audiometry and ABR test)
- Ophthalmology evaluation (visual acuity, retinal examination, corneal examination)
- Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)
- Cardiology evaluation (ECG, Echocardiogram)
- Skeletal survey (hips/pelvis: AP pelvis radiograph, Lower extremities: standing AP radiographs and spine X-ray)
- Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.

Enzyme replacement therapy (ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:

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

Vimizim® (Elosulfase alfa)[5-7]

- **Dose:** 2 mg/kg (IV) once weekly.

- **Strength:** 5 mL (5mg/5mL), single-use vials.
  Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 4 kg, give 10mg instead of 8mg.

- **Weight:** _____(kg): **calculated dose** _____(mg) IV.

- **Dilution:**

o For patients **<** 25 kg – dilute in 100 mL normal saline
o For patients **≥** to 25 kg – dilute in 250 mL normal saline

Administration of VIMIZIM® should be completed within 48 hours of dilution.

Special Precautions:
- Stable only in Normal Saline.
- The diluted Vimizim® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate[5,6]:

For less than 25 kg:
- 3 mL/hour for 15 minutes
- 6 mL/hour for 15 minutes
- 12 mL/hour for 15 minutes
- 18 mL/hour for 15 minutes
- 24 mL/hour for 15 minutes
- 30 mL/hour for 15 minutes
- 36 mL/hour for remainder of infusion (minimum of 3.5 hours)

For equal or more than 25 kg:
- 6 mL/hour for 15 minutes
- 12 mL/hour for 15 minutes
- 24 mL/hour for 15 minutes
- 36 mL/hour for 15 minutes
- 48 mL/hour for 15 minutes
- 60 mL/hour for 15 minutes
- 72 mL/hour for remainder of infusion (minimum of 4.5 hours)

The total volume of the administration should be delivered in approximately 3.5 - 4.5 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 VIMIZIM® infusion.

Side 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 Vimizim® 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.

Immunogenicity:[5]

As with all therapeutic proteins, there is potential for immunogenicity. All patients treated with VIMIZIM® 2 mg/kg once per week in the placebo-controlled trial developed anti-drug antibodies by Week 4. Anti-drug antibody titers were sustained or increased for the duration of VIMIZIM® treatment. Because all patients developed anti-drug antibodies, associations between antibody titers and reductions in treatment effect or the occurrence of anaphylaxis or other hypersensitivity reactions could not be determined.

All patients treated with VIMIZIM® 2 mg/kg once per week tested positive for neutralizing antibodies capable of inhibiting the drug from binding to the mannose-6-phosphate receptor at least once during the trial. Binding to this receptor is required for VIMIZIM® to be taken into cells where it is active. Neutralizing antibody titers were not determined in the patients. Therefore, the possibility of an association between neutralizing antibody titer and treatment effect cannot be assessed.

Assessment of the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including: assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VIMIZIM® with the incidence of antibodies to other products may be misleading.

Table 4: Monitoring the response to enzyme replacement therapy[4]

Assessment	Frequency
General	
Medical history Physical examination General appearance Neurological examination	Every visit
Lab Test	
CBC, diff Electrolytes Liver enzymes CPK level Bone profile and vitamin D levels	Every 3-6 months
General Examination	
Standardized upper extremity function test (Mallet test)	Annually
Hips and lower extremities	
Hips/pelvis: AP pelvis radiograph	As clinically indicated
Lower extremities: standing AP radiographs	As clinically indicated
Spine/spinal cord compression	
MRI of spine	Annually
radiograph spine	Every 1-3 year
ENT Evaluation	
Audiometry and ABR test	Annually

Assessment	Frequency
Ophthalmology Evaluation	
Visual acuity, retinal examination, corneal examination	As clinically indicated
Respiratory evaluation	
Chest X-ray, forced vital capacity, forced expiratory volume, sleep study	Annually
Cardiology Evaluation	
ECG, Echocardiogram	Every 1-3 years
Others	
Skeletal survey	Every 1-3 years
Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life	Annually
6MWT/T25FW	Annually

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Appendix II

The Mallet grading system for shoulder function.

Grade	Description
I	Flail shoulder
II	Active abduction ≤30° Zero degrees of external rotation Hand to back of neck impossible Hand to back impossible Hand to mouth with marked trumpet sign
III	Active abduction 30–90° External rotation up to 20° Hand to back of neck with difficulty Hand to back with difficulty Hand to mouth possible with partial trumpet sign (over 40° of shoulder abduction)
IV	Active abduction over 90° External rotation over 20° Hand to back of neck easy Hand to back easy Hand to mouth easy with less than 40° of shoulder abduction
V	Normal shoulder

Protocol for Mucopolysaccharidosis type VI (MPS VI) Patients Started on Naglazyme® (Galsulfase)

6

Background:

Definition:
Mucopolysaccharidosis VI , also known as Maroteaux–Lamy syndrome, is a clinically progressive disorder with a spectrum of mild to severe phenotypes.[1-3]

Causes:
The disease is caused by a deficiency in the lysosomal enzyme N-acetyl-galactosamine-4-sulfatase (also known as arylsulfatase B, ASB) due to a defect in ARSB gene coding for that enzyme; as a result, the cells of affected individuals are either unable to produce the enzyme or produce it in low amounts. This results in an inability of the lysosome to effect the stepwise degradation of the glycosaminoglycans (GAGs) dermatan sulfate, which are important constituents of the extracellular matrix, joint fluid, and connective tissue throughout the body. Because the disease is rare, and early symptoms can mimic other more common disorders, MPS VI is often under recognized and diagnostic delays are common.[1-3]

Clinical features:
Patients with rapidly progressing disease often have short stature with coarse facial features, joint and skeletal abnormalities, spinal cord compression, compromised cardiovascular and pulmonary function, corneal clouding, recurrent respiratory and ear infections, and early mortality in the late teens to early twenties, often from cardiopulmonary failure. MPS VI patients present with classical symptoms by 6–24 months of age. Although symptoms may appear later in life in those with slowly progressing disease, these patients nonetheless demonstrate severe morbidity and early mortality by the third to fifth decade of life. The patients often require clinical interventions related to one or more organ dysfunction such as corneal transplants, cardiac valve replacement, hip replacement, or spinal cord decompression surgery by their late teen to adult years. Although MPS VI patients do not typically exhibit neurocognitive deficits, physical limitations particularly with decreased sight and hearing can affect learning and development.[1-3]

Diagnosis:
Usually by findings of high dermatan sulfate in urine mucopolysaccharide analysis. The diagnosis is confirmed by deficiency of the enzyme on dried blood spot or white blood cell and DNA molecular testing of ARSB gene.[1-3]

Treatment:
Includes symptom-based interventions, enzyme replacement therapy with Naglazyme® (Galsulfase) and hematopoietic stem cell transplantation (particularly very young, severely affected patients).[1-3]

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

- Height, weight, head circumference
- Blood pressure
- Enzyme activity level
- DNA molecular testing for IDUA gene
- IgG antibody test
- CBC, diff
- Chemistry (electrolytes, BUN, serum creatinine)
- Liver enzymes
- CPK level
- Bone profile and vitamin D levels
- Urine for mucopolysaccharides
- Urine analysis
- Neurology evaluation
- MRI of brain and spine
- Median nerve conduction velocity
- Cognitive testing [developmental quotient (DQ) or intelligence quotient (IQ)]
- ENT evaluation (audiometry and ABR test)
- Ophthalmology evaluation (visual acuity, retinal examination, corneal examination)
- Respiratory evaluation (Chest X-ray, forced vital capacity, forced expiratory volume, sleep study)
- Cardiology evaluation (ECG, Echocardiogram)
- Skeletal survey
- Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound.
- Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.
- 12-minute walking test (12MWT) and 3-minute stair climb (3MSC)

Enzyme replacement therapy (ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:
- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1 mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1 mg/kg) IV; _____ (mg) IV.

Naglazyme® (Galsulfase)[4,5]

- **Dose:** 1 mg/kg (IV) once weekly.

- **Strength:** 5mL (5 mg/5mL), single-use vials.
  Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 14 kg, give 15 mg instead of 14 mg.

- **Weight:** _____(kg): **calculated dose**_____(mg) IV.

- **Dilution:**

o For patients **≤** to 20 kg – dilute in 100 mL normal saline
o For patients **>** 20 kg – dilute in 250 mL normal saline

Special Precautions:
- Stable only in Normal Saline.
- The diluted Naglazyme® solution should be filtered through a 0.2µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate[4,5]:

For less than or equal to 20 kg:
3 mL/hour for the first hour. If the infusion is well tolerated, the infusion rate can be increased to 32 mL/hour for approximately 3 hours.

For more than 20 kg:
The initial infusion rate should be 6 mL/hour for the first hour. If the infusion is well tolerated, the rate of infusion may be increased to 80 mL/hour for the remaining 3 hours.

The total volume of the administration should be delivered in no less than 4 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 Naglazyme® infusion.

Side Effects:
Most common: headache, fever, arthralgia, vomiting, upper respiratory infections, abdominal pain, diarrhea, ear pain, cough, and otitis media. Others: anaphylaxis and allergic reactions, infusion-related reactions.

Note:
- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Naglazyme® 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.

Table 5: Monitoring the response to enzyme replacement therapy[3,6]

	Every 6 months	Every 12 months	Every Other Year
General			
Medical history Physical examination General appearance	x		
Lab Test			
CBC, diff Electrolytes Liver enzymes CPK level Bone profile and vitamin D levels	x		

	Every 6 months	Every 12 months	Every Other Year
Neurology			
MRI of brain and spine			x
Median nerve conduction velocity			x
Cognitive testing [developmental quotient (DQ) or intelligence quotient (IQ)]		x	
ENT Evaluation			
Audiometry and ABR test		x	
Ophthalmology Evaluation			
Visual acuity, retinal examination, corneal examination		x	
Respiratory Evaluation			
Chest X-ray, forced vital capacity, forced expiratory volume, sleep study		x	

	Every 6 months	Every 12 months	Every Other Year
Cardiology Evaluation			
ECG, Echocardiogram			x
Others			
Skeletal survey			x
Abdominal CT or MRI to determine the spleen and liver volume. If not available, then, abdominal ultrasound.			x
Functional outcome measurements: MPS Health Assessment Questionnaire, or other tools exploring functional ability and quality of life.		x	
12-minute walking test (12MWT) and 3-minute stair climb (3MSC)		x	

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

Background:

Definition:
Fabry disease is an X-linked inborn error of glycosphingolipid catabolism. It is multisystem Lysosomal storage disease and it has other names including: Anderson-Fabry Disease or Alpha-Galactosidase A Deficiency.[1,2]

Causes:
The disease is caused by a defect in the gene coding for the lysosomal enzyme alpha-Galactosidase A (GLA 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 glycosphingolipids, mainly globotriaosylceramide (GL-3), in body fluids, in the lysosomes of endothelial and smooth-muscle cells of blood vessels, in ganglion cells, and in many cell types in the heart, kidneys, eyes, and most other tissues.[1,2]

Clinical features:
In classically affected males the following signs should appear as follow:

1. Acroparesthesias: onset of symptoms usually occurs in childhood or adolescence with periodic crises of severe pain in the extremities.

2. Angiokeratomas: the appearance of vascular cutaneous lesions, dark red to blue-black angiectases in the superficial layers of the skin. The lesions may be flat or slightly raised and do not blanch with pressure. The clusters of lesions are most dense between the umbilicus and the knees; they most commonly involve the hips, back, thighs, buttocks, penis, and scrotum, and tend to be bilaterally symmetric.

3. Anhydrosis or hypohidrosis.

4. Cornea verticillata: The characteristic corneal and lenticular opacities. Observed only by slit-lamp examination.

5. Cardiac and/or cerebrovascular disease is present in most males with the classic phenotype by middle age. Mitral regurgitation may present early in childhood. Left ventricular hypertrophy, valvular involvement, and conduction abnormalities are early findings. ECG changes including ST segment changes, T-wave inversion, and dysrhythmias such as a short PR interval and intermittent

supraventricular tachycardias may be caused by infiltration of the conduction system.

6. Cerebrovascular manifestations result primarily from multifocal small vessel involvement and may include thrombosis, transient ischemic attacks (TIA), basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, or frank cerebral hemorrhage and stroke.

7. Renal involvement: Progressive glycosphingolipid accumulation in the kidney interferes with renal function, resulting in azotemia and renal insufficiency.

8. Other features:
   a. GI involvement: may cause episodic diarrhea, nausea, vomiting, bloating, cramping abdominal pain, and/or intestinal malabsorption
   b. Pulmonary: Several affected individuals have had pulmonary involvement, manifest clinically as chronic bronchitis, wheezing, or dyspnea.
   c. Vascular: Pitting edema of the lower extremities may be present in adulthood in the absence of hypoproteinemia, varices, or other clinically significant vascular disease
   d. Cranial nerve VIII involvement: High-frequency hearing loss, tinnitus, and dizziness have been reported.
   e. Psychological: Depression, anxiety, severe fatigue, and other psychosocial manifestations lead to decreased quality of life in many affected individuals.

Heterozygous females can be as severely affected as hemizygous males, although the range of symptoms varies widely. A frequent clinical finding in females is the characteristic whorl-like corneal epithelial dystrophy observed by slit-lamp examination (cornea verticillata).[1-3]

Diagnosis:
The diagnosis is suspected when there is clinical findings and an increase of plasma (lyso) Gb3. It is confirmed by deficiency of the enzyme on dried blood spot or white blood cell or cultured fibroblasts. The diagnosis is confirmed by DNA molecular testing of GLA gene. However, the possibility of a pseudodeficiency of the enzyme should be considered. Of note, many carrier females have normal alpha-Gal A enzyme activity and the diagnosis is only achieved by molecular testing.

Table 6: Diagnostic criteria for Fabry disease[4, 5]

Males	Females
GLA mutation	GLA mutation
+	+
AGAL-A deficiency of ≤ 5% of mean reference value in leukocytes	Normal or deficient AGAL-A in leukocytes
+	+
A or B or C	
A	
≥ 1 characteristic FD sign/symptom (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma	
B	
Increase of plasma (lyso) Gb3 (within range of males with definite FD diagnosis)	
C	
A family member with a definite FD diagnosis carrying the same GLA mutation	
Uncertain diagnosis of FD (Males/Females)	
All patients presenting with a non-specific FD sign (such as LVH, stroke at young age, proteinuria) who do not fulfil the criteria for a definite diagnosis of FD have a GLA variant of unknown significance. Further evaluations are needed, following diagnostic algorithms	
Gold standard for uncertain FD diagnoses	
In subjects with an uncertain FD diagnosis, the demonstration of characteristic storage in the affected organ (e.g. heart, kidney, aside from skin) by electron microscopy analysis, according to the judgment of an expert pathologist, in the absence of medication that can lead to storage, confirms FD	

Treatment:
Includes symptom-based interventions, enzyme replacement therapy with Replagal®(Agalsidase-alpha) or Fabrazyme®(Agalsidase-beta).[1-3]

Baseline assessments and investigations prior to initiation of enzyme replacement therapy (ERT)[6]:

- ***General:***
    - o Height, weight, head circumference
    - o Blood pressure
    - o Pain score (Brief Pain Inventory-BPI)
    - o Age appropriate Quality of Life score (SF-36 or EQ5D)
    - o Severity Score Index – MSSI (Whybra et al 2004)7
- ***Cardiac:***
    - o ECG
    - o 24 hours Holter monitor
    - o Echocardiogram
- ***Renal:***
    - o Assess Glomerular filtration rate (GFR) by Tc99m MAG3 (mercaptoacetyltriglycine) or Tc99m-DTPA (diethylenetriaminepentacetate).
    - o Urine analysis
    - o 24 Hour urine protein
    - o Spot urine Alb/Creatinine ratio
    - o Renal biopsy- at the discretion of the renal physician
- ***Neurology:***
    - o MRI brain examination
    - o quantitative sudomotor axon reflex testing (QSART) assessment of sweating (where available)
    - o EMG where neuropathy clinically apparent
- ***Opthalmology:***
    - o Slit-lamp examination (cornea verticillata)
    - o Retroillumination (AFD cataract)
    - o Retinal examination (vascular abnormalities)
- ***Audiology:***
    - o Pure tone audiogram
- ***Laboratory Investigations:***
    - o Full blood count
    - o Urea & electrolytes
    - o Liver function tests
    - o Fasting lipid profile
    - o Plasma Gb3 (globotriaosylceramide)
    - o Enzyme activity level
    - o DNA molecular testing for GLA gene
- ***Urine***
    - o Albumin/creatinine ratio
    - o Urine Gb3

Table 7: Consensus criteria for initiation of ERT[5]

	No signs or symptoms	Renal	Cardiac	CNS	Pain	GI
Classical FD, Males	if ≥ 16 years of age	1. Microalbuminuria 2. Proteinuria 3. Renal insufficiency (GFR:45-90)	1.Cardiac hypertrophy (Maximal Wall Thickness > 12 mm)without (or only minimal signs of fibrosis) 2. Signs of cardiac rhythm disturbances	1. White matter lesions 2. Transient ischemic attack / Stroke 3. Hearing loss	Neuropathic pain	GI symp-toms
Non-classical FD, Males		Same except Renal	Same	Same	Same	Same
Classical FD, Females	Same as classical male					
Non-classical FD, Females	Same as classical male					

Consensus criteria for NOT starting ERT[5]:

1. Advanced cardiac disease with extensive fibrosis
2. End stage renal disease, without an option for renal transplantation, in combination with advanced heart failure
3. End stage FD or other comorbidities with a life expectancy of < 1 year
4. Severe cognitive decline of any cause
5. Very mild disease

Consensus criteria for stopping ERT[5]:

1. Non-compliance > 50% of infusions
2. Failure to attend regularly (according to local guidelines) at follow up visits
3. Persistent life threatening or severe infusion reactions that do not respond to prophylaxis, e.g. anaphylaxis
4. Patient request
5. End stage renal disease, without an option for renal transplantation, in combination with advanced heart failure
6. End stage FD or other comorbidities with a life expectancy of < 1 year
7. Severe cognitive decline of any cause
8. Lack of response for 1 year when the sole indication for ERT is neuropathic pain while receiving maximum supportive care

Enzyme replacement therapy(ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:

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

Replagal™ (Agalsidase alfa)[8]

- **Dose:** 0.2 mg/kg (IV) every 2 weeks.
- **Strength:** 3.5mg/3.5mL, single-use vials.
- Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 30 kg, give 7 mg instead of 6 mg.
- **Weight:** _____(kg): **calculated dose**_____(mg) IV.

• **Dilution:**
Dilute the total volume of Replagal® concentrate required in 100 mL normal saline

Infusion Rate:[8]
- Infuse over 40 minutes using a dedicated IV line with filter. Do not infuse other agents through same IV line.
- Interrupt infusion in the presence of infusion-related reactions (eg, chills, flushing, dyspnea, rigors, tachycardia, urticaria). Infusion may be restarted after 5-10 minutes if symptoms subside or after administration of analgesics, antipyretics, antihistamines, and/or corticosteroids.

The total volume of the administration should be delivered in approximately 40 minutes.

(OR)

Fabrazyme® (Agalsidase beta)[9]

• **Dose:** 1 mg/kg (IV) every 2 weeks.

• **Strength:** 5mg and 35mg, (5mg/mL), single-use vials.

• Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 32 kg, give 35 mg instead of 32 mg.

• **Weight:** _____(kg): **calculated dose** _____(mg) IV.

• **Dilution:**

Recommended Minimum Volumes for Dilution	
Patient weight (kg)	Minimum total volume (mL)
< 35	50
35.1 - 70	100
70.1 - 100	250
> 100	500

Special Precautions:
- Stable ONLY in Normal Saline.
- The diluted Replagal® or Fabrazyme® solution should be filtered through a 0.2µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion Rate[9]:
- IV: Initial infusion not to exceed 15 mg/hour (0.25 mg/minute); after patient tolerance to initial infusion rate is established, the infusion rate may be increased in increments of 3 to 5 mg/hour (0.05 - 0.08 mg/minute) with subsequent infusions.

- Per the manufacturer's recommendation:

  For patients weighing **<** 30 kg, the maximum infusion rate should remain at 0.25 mg/min.

  For patients weighing **≥** 30 kg, the administration duration should not be less than 1.5 hours (based upon individual tolerability).

  An initial maximum infusion rate of 0.01 mg/minute should be used for rechallenge in patients with IgE antibodies; may increase infusion rate (doubling the infusion rate every 30 minutes) to a maximum rate of 0.25 mg/minute as tolerated.

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 infusion.

Side Effects:
Anaphylaxis and allergic reactions, infusion reactions, and immune mediated reactions, Very common adverse reactions included chills, pyrexia, feeling cold, nausea, vomiting, headache and paraesthesia.

Note:
- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Replagal® or Fabrazyme® 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.

Table 8: Monitoring the response to enzyme replacement therapy[5,6]

	Every 3 months	Every 12 months
General		
Medical history Physical examination General appearance	x	
Pain score	x	
Quality of Life score (SF-36 or EQ5D)	x	
Mainz Severity Score Index	x	
Lab Test		
CBC, diff Electrolytes Liver enzymes CPK level Bone profile and vitamin D levels Fasting lipid profile	x	
IgG and IgE antibody testing		x
Plasma Gb3		x
Urine Test		
Urine analysis	x	
Albumin/Creatinine ratio	x	
Urine Gb3		x
GFR and 24 hour urinary protein		x
Neurology		
MRI of brain		x

	Every 3 months	Every 12 months
ENT Evaluation		
Audiometry and ABR test		x
Ophthalmology Evaluation		
Visual acuity, retinal examination, corneal examination		x
Cardiology Evaluation		
ECG, 24 hour holter monitor, Echocardiogram		x

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Protocol for Gaucher Disease Patients Started on Cerezyme®

(Imiglucerase)

Background:

Definition:

Gaucher disease 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 in GD 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:
It is confirmed by deficiency of the enzyme on dried 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 patients 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]

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 temperature
- 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 (1 mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1 mg/kg) IV; _____ (mg) IV.

Cerezyme®: Imiglucerase [4]

- **Dose:** Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week up 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 and rate of progression may dictate that treatment be initiated at a relatively high dose or relatively frequent administration.[4]

- **Strength:** 200 units or 400 units, lophilized powder for reconstitution. Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example, if the patient weighs 4 kg, give 200 units instead of 240 units .

- **Weight:** _____(kg): **calculated dose** _____(mg) IV.

- **Dilution:** dilute with NS to a final volume of 100 to 200 mL

- **Administration:** Infuse over 1 to 2 hours (given intravenously)

Special Precautions:
- Stable ONLY in Normal Saline.
- The diluted Cerezyme® solution should be filtered through a 0.2 μm, low protein-binding, in-line filter during administration to remove any visible particles.

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.

Side Effects:
Anaphylaxis, allergic reactions, infusion reactions, and immune mediated reactions, headache, N/V, abdominal pain, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and tachycardia.

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.

Table 9: 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
	PT and PTT in patient with bleeding symptoms							
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		

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