Anderson-Fabry disease: recommendations for its diagnosis, management and treatment in South Africa, 2014

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Introduction

Fabry or Anderson-Fabry disease (AFD) is a rare, X-linked lysosomal storage disorder, characterised by the accumulation of globotriasylceramide (GL3) in tissues throughout the body.1 Deficiency of the lysosomal enzyme α-galactosidase A (α-gal A) is responsible for the disorder. The gene for α-gal A is located at chromosome Xq22 and many mutations have been identified.1 The disease usually presents in childhood, is progressive and multisystem, and results in increasing disability and premature death.1

Women with a mutation of the α-gal A gene often display significant disease, but their disease onset tends to be later in life, and their disease progression is usually less severe. This variability in disease severity is explained by random X chromosome inactivation.1 Whereas treatment was previously entirely symptomatic, the heterogeneity and complexity of this disorder, as well as the availability of enzyme replacement therapy (ERT), has made the creation of explicit guidelines on the diagnosis, assessment, treatment and follow-up of patients and their families necessary.1

These guidelines were established by a medical advisory board consisting of physicians from across South Africa who are involved in the direct care of the affected individuals, and/or who can provide specialised expertise to treating physicians in local communities. These guidelines will assist individual physicians with the care of their patients by providing a source of collective knowledge and experience. In addition, these recommendations will provide guidance for medical insurance companies, medical aids and governmental organisations when planning the provision of care.
for these patients. Previous clinical studies, published material, and established 2005 AFD treatment guidelines from the UK, as well as more recent publications, were reviewed by the group and discussed at the Lysosomal Storage Disease Medical Advisory Board meetings, which took place in Johannesburg from 7 August 2010.

**Overview**

AFD is a rare, X-linked lysosomal storage disorder (LSD), caused by an inborn deficiency of α-gal A. AFD is the second most common of the 40 LSDs, after Gaucher’s disease, with an incidence of 1:117 000 in Australia and 1:468 000 in the Netherlands. It occurs in all population and racial groups.

The gene for α-gal A is located at chromosome Xq22, and more than 400 mutations have been identified. The mutations are usually “private” (restricted to a single or few families) and commonly lead to complete lack of detectable enzymes. The inheritance of AFD follows an X-linked pattern. Hemizygous males carry a defective gene on the X chromosome and develop classical AFD. Heterozygous females have one normal and one abnormal allele of this gene. Usually, they have milder disease with a later onset than that for hemizygous males. However, a number of studies have demonstrated a significant burden of disease in females.

The deficiency of α-gal A results in an inability to catabolise glycosphingolipids, with the progressive accumulation of GL3 in the lysosomes of the endothelial cells, vascular smooth muscle, erector pili muscles in the skin, myocardium, corneal epithelial cells and in organs such as the kidney, pancreas, bowel and lungs. Early manifestations appear around age 10 years in males and several years later in females. The symptoms of acute neuropathic pain episodes in the hands and feet, hypohidrosis or anhidrosis, sensory loss, gastrointestinal disturbances and intolerance to heat, cold and exercise reflect damage to the small nerve fibres of the peripheral and autonomic nervous system.

Early renal manifestations may include microalbuminuria and proteinuria. Further disease progression results in declining glomerular filtration rate (GFR), interstitial scarring, glomerulosclerosis, tubular atrophy, and ultimately end-stage renal disease. Cardiovascular symptoms may include sinus node dysfunction, conduction abnormalities and arrhythmia, left ventricular hypertrophy, valvular dysfunction, angina pectoris, myocardial infarction and heart failure. Cerebrovascular involvement can result in disturbed concentration, dizziness, dementia, headaches and learning difficulties; an early stroke and/or transient ischaemic attack (TIA), as well as thrombosis or cerebrovascular haemorrhages. Respiratory symptoms, such as dyspnoea and significant airflow obstruction, have been described in up to 61% of patients with the classical form of AFD. Chronic depression occurs in up to 46% of AFD patients, and can be exacerbated by limitations to their quality of life as their physical, social and job performance deteriorates with the progression of their disease symptoms.

Although clinically variable, classical AFD is usually a progressive disease, in which the signs and symptoms change as the patient ages. The main causes of death are renal failure, heart disease or a stroke around the age of 50 years for hemizygous men and 70 years for obligate carrier women.

**Clinical features**

**Childhood and adolescence (≤ 16 years)**

The most common clinical features are acroparaesthesiae, pain and AFD “crises” in childhood and adolescence. Angiokeratomas are found more frequently with increasing age. Ophthalmological abnormalities, especially cornea verticillata (Figure 1) should be actively sought. Hearing impairment occurs occasionally, and its presence can be considered a reason to start treatment. Dyshydrosis, i.e. hypohydrosis and anhidrosis, which can lead to a heat stroke, impairs quality of life. A history of non-specific bowel disturbances can lead to the consideration of other diagnoses. Lethargy and tiredness are frequent non-specific complaints in AFD.

This characteristic whorl or radial pattern is visible using a slit lamp in most Fabry patients and asymptomatic female carriers. Image used with permission, from R.J. Desnick, PhD, MD

**Figure 1: Cornea verticillata**

**Early adulthood (17-30 years)**

The angiokeratomas become more extensive in early adult life. Proteinuria, lipiduria and haematuria indicate progressive renal involvement. Oedema, fever, hypohydrosis or anhidrosis, lymphadenopathy, heat sensitivity, diarrhoea and non-specific abdominal pain are commonly found in this age group.

**Later adulthood (age > 30 years)**

Heart disease, impaired renal function, and a stroke or TIA are frequently found in later life.
Description of the clinical features

Pain
Neuropathic pain typically appears during childhood.1 It may be chronic or experienced as episodic AFD “crises” or acroparaesthesia. An excruciating burning sensation in the palms and soles, often radiating to the proximal extremities, and occasionally to the abdomen, is how patients describe the pain. AFD pain may occur spontaneously, but is exacerbated by temperature changes, fever, stress, physical exercise and alcohol.

Angiokeratomas
Angiokeratomas are small, raised, dark red spots. They may be absent in patients with atypical AFD.13 Lesions develop slowly in the bathing trunk area, i.e. the genitalia, scrotum, buttocks and inner thighs, around the umbilicus, on the back and around the mouth.1

Hypohidrosis
Hypohidrosis, or occasionally anhidrosis, is common in male patients and causes heat intolerance. Patients do not tolerate exercise well, and may suffer nausea, dyspnoea, lightheadedness and headaches, or complete collapse with loss of consciousness, i.e. a heat stroke. The reduced production of tears and saliva also occurs.14

Sensory organs
Eyes
The eyes are affected in most AFD patients,15 and cornea verticillata, a cream-coloured, whorl-shaped opacity, is diagnostic (Figure 1). A posterior subcapsular cataract also occurs, as do tortuous vascular lesions on the retina and conjunctiva. Severe visual loss can be a consequence.

Ears
High-frequency sensorineural hearing loss is common,16 and other audiovestibular symptoms, i.e. tinnitus and vertigo,7,17 may be present.

Gastrointestinal symptoms
The gastrointestinal symptoms of AFD tend to occur after meals, and comprise recurrent bouts of abdominal pain in the mid and lower abdomen.1 Nausea, vomiting, abdominal distension, bloating, flatulence, episodic diarrhoea and constipation may all occur.

Renal function
Impairment of renal function is common in classical AFD, and is an important cause of death. Proteinuria, haematuria, nephrotic syndrome and eventual chronic renal failure requiring dialysis and/or renal transplantation4,7,18 are the usual renal findings. Albuminuria, proteinuria and chronic kidney disease are common elements of a progressive AFD nephropathy. An estimated GFR of < 60 ml/minute/1.73 m2 was recorded in 45% of males and 20% of females aged 40 years and older.4 The age of onset of end-stage renal failure is usually in the 30s for hemizygous males, but it may start in childhood. Heterozygous females can develop substantial renal AFD symptoms and are at risk of premature death.4

Cardiac function
Left and right ventricular hypertrophy, an enlarged left atrium, heart valve abnormalities, atrial arrhythmia and conduction disturbance are the typical findings of cardiac involvement. Cardiac involvement may be the only symptom in some hemizygous males,1,7,13 and 4% of males with hypertrophic cardiomyopathy may have a “cardiac” variant19 of AFD.

Nervous system (central nervous and peripheral nervous systems)
TIA or a stroke affects 15-20% of AFD patients, frequently recur, and have a poor prognosis.10 Disturbed concentration, dizziness, dementia, headaches and learning difficulties are other central nervous system (CNS) symptoms that occur.7 The peripheral nervous system may also be affected, with disturbances of touch, pain and sensitivity to temperature. Chronic depression, in up to 46% of the AFD patients, can be complicated further by limitations to their quality of life as their physical, social and job performance deteriorates with disease progression.11

Respiratory function
Significant airflow obstruction is common in patients with AFD, and smoking is particularly inadvisable as it seriously exacerbates pulmonary impairment.4

Diagnosis
As with any rare disorder, identification of the symptoms early is paramount to effective diagnosis. The clinical features set out in this document provide the basis for suspecting AFD.

Affected males can be confidently diagnosed, and the diagnosis can be excluded in males by enzyme studies. Heterozygous females are seldom identified by enzyme studies, and need to have the disease identified by genetic (DNA) studies.1 Identification of the causative mutation in an affected male enables the identification of heterozygous females within that family. The early testing of males and females in such families for the mutation will distinguish those individuals not needing regular follow-up from those who are affected and who require careful follow-up and treatment.20

Enzyme studies are available in South Africa at the Serogenetics Laboratory, Division of Human Genetics, National Health Laboratory Service, Johannesburg. Liaison with the laboratory before sending specimens is recommended because specimens should be kept cool, but not frozen. Five to 10 ml in an acid-citrate-dextrose
Guidelines: Anderson-Fabry disease

Specimen tube is required for enzyme analysis. Ideally, blood from an unaffected male should be sent with the specimen from the patient. This will prevent false positive results owing to low activity from poor transport conditions. Enzyme analysis is also available on dried blood spot specimens at a European laboratory. This analysis is made available by Genzyme Corporation and Shire Human Genetic Therapies (Pharmaplan, Johannesburg). Mutation analysis is not available in South Africa, but local medical genetics units can facilitate analysis at laboratories in other countries.

**Differential diagnoses**

AFD is a progressive multisystem disorder. The initial symptoms can be non-specific and even vague, especially in the paediatric population. From the description of symptoms and signs, it can be appreciated that the symptoms can be non-specific, and even confusing, unless a high index of suspicion is entertained. There is a mean delay between the first symptoms and diagnosis of 13.7 years in males and 16.3 years in females. Diseases that are often considered instead of AFD are listed in Table I.

**Recommended initial evaluation and investigations**

The clinical and laboratory testing recommended at the initial evaluation is set out in Table II.

**Treatment and care**

AFD therapy comprises both the specific replacement of the deficient α-gal A (ERT) and supportive or adjunctive therapy of complications of the disorder. Adjunctive therapies include the treatment of pain, hypertension, renal disease, cardiac disease, CNS involvement and

### Table I: Differential diagnoses of Anderson-Fabry disease

<table>
<thead>
<tr>
<th>Features of Anderson-Fabry disease</th>
<th>Misdiagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiokeratoma</td>
<td>Petechiae of meningococcal meningitis, hereditary haemorrhagic telangiectasia, Fordyce disease, Schindler disease, fucidosis and siaidosis</td>
</tr>
<tr>
<td>Pain</td>
<td>Rheumatoid arthritis, rheumatic fever, Raynaud’s disease and “growing pains”</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Glomerulonephritis, pyelonephritis and exposure to silica dust</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>Hypertrophic or restrictive cardiomyopathy, congestive cardiac failure and coronary artery disease</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Irritable bowel syndrome and pancreatic insufficiency</td>
</tr>
<tr>
<td>Cornea verticillata</td>
<td>Amiodarone or chloroquine therapy</td>
</tr>
</tbody>
</table>

### Table II: Initial and follow-up evaluations of patients with Anderson-Fabry disease

<table>
<thead>
<tr>
<th>System</th>
<th>Investigation</th>
<th>Initial evaluation</th>
<th>Frequency at follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Medical and general history</td>
<td>X</td>
<td>6 monthly</td>
</tr>
<tr>
<td></td>
<td>Family pedigree</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of concomitant medications</td>
<td></td>
<td>Each infusion</td>
</tr>
<tr>
<td></td>
<td>Clinical examination</td>
<td>X</td>
<td>3 monthly</td>
</tr>
<tr>
<td></td>
<td>Vital signs</td>
<td>X</td>
<td>Each infusion</td>
</tr>
<tr>
<td></td>
<td>Pain score (PBI)</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>Quality of life score (age appropriate), i.e. SF-36 or EQ5D</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>Mainz Severity Score Index21</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>Adverse event recording</td>
<td></td>
<td>Each infusion</td>
</tr>
<tr>
<td>Cardiac</td>
<td>ECG</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>24-hour ECG</td>
<td>X</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td></td>
<td>Echocardiogram</td>
<td>X</td>
<td>As clinically indicated, annually after age 35 years</td>
</tr>
<tr>
<td></td>
<td>Symptom-limtiting exercise testing</td>
<td></td>
<td>If clinically indicated</td>
</tr>
<tr>
<td>Renal</td>
<td>GFR</td>
<td>X</td>
<td>12 monthly, or as indicated</td>
</tr>
<tr>
<td></td>
<td>Spot urine albumin and creatinine ratio (first morning void)</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>Spot serum creatinine (morning)</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>Renal biopsy</td>
<td>At the discretion of the nephrologist</td>
<td></td>
</tr>
</tbody>
</table>
angiokeratoma, and should be available to all patients who are symptomatic. There are no randomised controlled trials on these adjunctive therapies in AFD, and the evidence for their effectiveness is largely derived from experience in other similar conditions. See Table III for examples of such therapies.

**Genetic counselling**

AFD is an X-linked inherited disorder that affect males and females. Genetic counselling by an appropriately trained healthcare professional is recommended for all patients and their immediate families. This enables the identification of at-risk individuals who may benefit from intervention. The identification of an index case can aid the expeditious diagnosis of other cases in the family. Given the X-linked mode of inheritance, it is important for patients to understand the possible implications for other family members and to explore the possibility of “cascade” screening.

**Enzyme replacement therapies**

AFD is a chronic, progressive disorder. The aim of ERT is to prevent or limit progression, and attempt to reverse or stabilise advanced disease. It is accepted that treatment is most likely to be successful when started early in the course of the disease. The manifestations responsive to ERT have been used to devise the criteria required for the initiation of therapy.

<table>
<thead>
<tr>
<th>System</th>
<th>Investigation</th>
<th>Initial evaluation</th>
<th>Frequency at follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurology</td>
<td>MRI of the brain</td>
<td>Optional</td>
<td>Annually, if abnormal, otherwise two yearly when there are new neurological events</td>
</tr>
<tr>
<td></td>
<td>Assessment of seating</td>
<td>If available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EMG</td>
<td>When neuropathy is suspected</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Spirometry</td>
<td>If indicated</td>
<td>As indicated</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Silt-lamp [cornea verticillata]</td>
<td>X</td>
<td>As indicated</td>
</tr>
<tr>
<td></td>
<td>Retinoulationation (cataract)</td>
<td>X</td>
<td>As indicated</td>
</tr>
<tr>
<td></td>
<td>Retinal examination (vascular abnormalities)</td>
<td>X</td>
<td>As indicated</td>
</tr>
<tr>
<td>Audiology</td>
<td>Pure tone audiogram</td>
<td>X</td>
<td>12 monthly</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Full blood count</td>
<td>X</td>
<td>As indicated</td>
</tr>
<tr>
<td></td>
<td>Urea, creatinine and electrolytes, and eGFR</td>
<td>X</td>
<td>As indicated, at least 12 monthly</td>
</tr>
<tr>
<td></td>
<td>Liver function tests</td>
<td>X</td>
<td>As indicated</td>
</tr>
<tr>
<td></td>
<td>Fasting lipid profile</td>
<td>X</td>
<td>As indicated</td>
</tr>
<tr>
<td></td>
<td>Plasma GL3 (freeze serum for later use)</td>
<td>When available</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>α-gal A antibodies</td>
<td>On initiation of ERT</td>
<td>When indicated, at the start of new therapy</td>
</tr>
<tr>
<td>Urine</td>
<td>Albumin to creatinine ratio</td>
<td>As above</td>
<td>12 monthly</td>
</tr>
<tr>
<td></td>
<td>Urine GL3 (10 ml frozen)</td>
<td>As above</td>
<td>12 monthly</td>
</tr>
</tbody>
</table>

Table III: Adjunctive therapies in Anderson-Fabry disease

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Avoidance of trigger activities</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine, gabapentin and phenytoin</td>
</tr>
<tr>
<td></td>
<td>Use nonsteroidal anti-inflammatory drugs with caution</td>
</tr>
<tr>
<td>Angiokeratoma</td>
<td>Argon laser therapy, if desired by the patient</td>
</tr>
<tr>
<td>Renal disease</td>
<td>ACE inhibitors in patients without renal artery stenosis</td>
</tr>
<tr>
<td></td>
<td>Angiotensin-receptor blockers</td>
</tr>
<tr>
<td></td>
<td>Dialysis or transplantation, as indicated</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Antianginal agents, i.e. beta blockers, calcium-channel blockers and nitrates</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Digoxin for heart failure</td>
</tr>
<tr>
<td>Dysrhythmias</td>
<td>Antiarrhythmic agents and anticoagulant medicine for tachyarrhythmias</td>
</tr>
<tr>
<td></td>
<td>A pacemaker for symptomatic bradycardia</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>Standard therapies, including statins</td>
</tr>
<tr>
<td>Hypertension</td>
<td>ACE inhibitors and other antihypertensive agents</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Statins</td>
</tr>
<tr>
<td>Neurovascular disease and TIA</td>
<td>Aspirin and clopidogrel</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme, TIA: transient ischaemic attack
Guidelines: Anderson-Fabry disease

Treatment should commence as soon as the symptoms or signs appear in males. It is anticipated that all males who have a pathogenic mutation will require ERT. The presence of a pathogenic mutation in females is not an indication for ERT on its own. However, the clinical criteria for commencing therapy in females should be the same as those in males. Asymptomatic patients must undergo a full clinical assessment and annual re-evaluation.

### Products and dosages

The dosage is as follows:

- **Agalsidase alpha**, at a dose of 0.2 mg/kg, intravenously, every two weeks. It is produced using a genetically engineered human sarcoma fibroblast cell line. The product licences are based on the National Institutes of Health study.22
- **Agalsidase beta**, at a dose of 1 mg/kg intravenously, every two weeks. It was approved by the US Food and Drug Administration for use in the USA in 2003. It is produced in the Chinese hamster ovary cell line. The product licences are based on the Mount Sinai School of Medicine study group.23

Several other controlled studies, including an additional placebo-controlled outcome study, have been published.24-26

The dosages just described are those contained in the registration data. Researchers have compared the two products and found them to be equivalent, if administered at the same dose.27 Recent literature on treatment guidelines for the diagnosis and treatment of AFD have been published, and should be consulted for further information on general and organ-specific recommendations.4,7,20

### Indications for enzyme replacement therapy

**Pain** is often a first manifestation of the disease, and therapy started at this stage is also intended to arrest the progression and involvement of other organ systems. The indications for ERT are set out in Table IV.

**Boys** who are asymptomatic aged 10-13 should be considered for ERT, and treatment initiated by 16 years of age.7 The duration of treatment is usually lifelong, except where indications for cessation of therapy are present.

**Administration of enzyme replacement therapy**

**Treatment regimens**

Patients are offered either agalsidase alpha or agalsidase beta. The infusion rate is dependent on the protein load and dose.

The treatment regimens of either agalsidase alpha or agalsidase beta should be used according to their respective prescribing information.1 Mixing and administration documents included in the package inserts need to be read by the treating physician prior to using the product. Premedication with paracetamol and/or an antihistamine should be given at the discretion of the prescribing clinician. Hydrocortisone may be used, as indicated. The first five doses of enzyme replacement should be given in hospital, with full monitoring and resuscitation facilities available. If an infusion reaction occurs, then further doses should be given in hospital with premedication, as described. When the clinician

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**Table IV: Indications for enzyme replacement therapy**

<table>
<thead>
<tr>
<th>General symptoms of Anderson-Fabry disease</th>
<th>Evidence of renal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain interfering with quality of life</td>
<td>GFR (&lt; 80 ml/minute)</td>
</tr>
<tr>
<td>Evidence of cardiac disease</td>
<td>Left ventricular hypertrophy on ECG</td>
</tr>
<tr>
<td>Evidence of neurovascular disease</td>
<td>A previous stroke or TIA</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Symptoms significantly altering quality of life</td>
</tr>
</tbody>
</table>

**The following are indications for ERT in boys:**

<table>
<thead>
<tr>
<th>General</th>
<th>ENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor growth that is unexplained</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Significant symptoms affecting quality of life</td>
<td>Episodic vertigo</td>
</tr>
</tbody>
</table>

**The following are indications for ERT in women:**

<table>
<thead>
<tr>
<th>General</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria or microalbuminuria</td>
<td>Proteinuria or microalbuminuria</td>
</tr>
</tbody>
</table>

|                   | Acroparathesia non-responsive to conventional treatment |
|                   | Persistent proteinuria of ≥ 300 mg/24 hours |
|                   | GFR below 80 ml/minute/1.73 m² |
|                   | Significant cardiac involvement |
|                   | Cerebrovascular involvement or TIA |
|                   | Other symptoms impacting significantly on the quality of life |

ECG: electrocardiogram, ENT: ear, nose and throat, ERT: enzyme replacement therapy, GFR: glomerular filtration rate, MRI: magnetic resonance imaging, TIA: transient ischaemic attack
is confident that infusions will proceed without serious or life-threatening reactions at a specific infusion rate, then patients may be offered alternative options, such as outpatient or home infusion therapy. This should be initiated by an accredited home care nursing service, but ultimately, the enzymes may be administered by the patients themselves after appropriate training. Restarting treatment after a break must be performed as for the initiation of treatment.

Limitations
ERT should be used with caution in pregnancy and lactation.1 The presence of another life-threatening illness or disease, where the prognosis is unlikely to be improved by ERT, should lead to careful consideration of the use thereof.

Safety and immunology of enzyme replacement therapy
ERT seems to be well tolerated by patients with AFD. Antibody formation frequency is dependent on the assay sensitivity, and has been reported to be approximately 50-90% for both enzyme preparations.28 Despite antibody formation being reported with both preparations, there is no clear evidence of any impact on the clinical efficacy of treatment.28

Infusion-associated reactions are the most common reactions in patients receiving ERT. As with any protein infusion, hypersensitivity reactions have been reported with both preparations. Agalsidase alpha infusion reactions occurred in 7-57% of patients,16,22 and most commonly consisted of rigors, pyrexia, flushing, headaches, nausea and dyspnoea. Agalsidase beta infusion reactions occurred in 55% of patients, compared to 23% in the placebo group.29 The most common infusion reactions are fever, chills, nausea, vomiting, headaches and paraesthesia. They relate to the infusion rate and amount of protein that needs to be infused. There seems to be no difference in the safety profile between both enzymes when studied in head-to-head trials, and at a dose of 0.2 mg/kg/2 weeks.31 The infusion duration needs to be extended, with increasing doses, based on the severity of the disease and desired treatment outcome. It is important to refer to the individual product labelling for details on complete safety information, as well as infusion and administration guidance. For the purposes of these guidelines, it is assumed that both preparations are available for prescription, and that patients will be offered a choice of products. Agalsidase alpha is registered in South Africa. Agalsidase beta is not currently registered in South Africa, but is available as a Section 21 medication.

Safety monitoring
A persistent reaction to enzyme infusion should be assessed by the clinician, and the existence of antibodies to α-gal A investigated. Anaphylactic-type reactions should be treated as a medical emergency, the infusions suspended and the existence of immunoglobulin E antibodies immediately investigated.1

Safety assessments

Safety end-points
Safety should be monitored by:1
- A clinical examination.
- The vital signs.
- Routine blood tests.

Adverse events
Adverse events should be categorised as infusion and non-infusion related, and scored as mild, moderate or severe. Infusion reactions should be managed by decreasing the infusion rate, and reducing the dose, premedication or even desensitisation, if needed. Adverse reactions should be reported to the supplier of the product.

Follow-up
The clinical and laboratory testing recommended during follow-up is set out in Table II.1

It should be noted that if found to be abnormal at baseline, GFR, electrocardiogram and magnetic resonance imaging of the brain in children should be performed, depending on the patient’s age and ability to co-operate.

Assessments
Efficacy end-points
Efficacy end-points are considered an improvement in or a prevention of deterioration in:1
- Renal function (defined by GFR, creatinine clearance or proteinuria).
- Pain scores.
- Age-appropriate quality-of-life measurement.
- Cardiac structure and function.
- Neurological status.
- Growth and development in children.
- Composite end-point, using a severity score index.

Annual assessment (objective evidence)
A specific assessment should be considered annually from the first anniversary of the start of ERT.1

It should consider objective evidence of progression in measured clinical criteria which are not:
- Attributable to a secondary pathology.
- Commensurate with natural age-related decline.
- Remediable by increasing the dose, changing the product or the institution of any other simple therapeutic measure.
Within the normal measured variation of that laboratory parameter.

Outweighed in clinical significance by stabilisation or improvement in one of the other criteria.

On the basis of current major criteria, disease progression might include:

- Worsening of pain beyond the baseline.
- Deterioration of the GFR > 1-3 ml/minute/year or proteinuria (20% decline).
- Progressive impairment of systolic or diastolic dysfunction, resulting in the worsening of heart failure symptoms.
- The new presentation of clinically significant neurovascular disease.

If there has been no change or a worsening of the symptoms after 6-12 months therapy, consider evaluating and monitoring the patient, as well as conducting an assessment of the clinical data.

If there is still no improvement:

- The reasons for this should be investigated, e.g. neutralising antibodies.
- The dose should be adjusted.
- A change could be made to an alternative enzyme product.
- Continue on same dose to allow more time for the treatment to have an effect.

**Treatment withdrawal**

**General**

Treatment withdrawal should be considered if the following general factors apply:

- There are intolerable and unavoidable adverse effects.
- There is intercurrent illness, where either the long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for AFD.
- At the request of the patient or properly allocated guardian acting in the patient’s best interests, if the patient is properly deemed not to be competent.
- If the circumstances of the patient’s lifestyle are such that sufficient compliance with treatment is not possible. Such cases might include intravenous drug abuse, associated with a peripatetic lifestyle.

**Specific**

Treatment withdrawal should be considered if the following specific factors apply:

- Objective evidence of progression that cannot be explained or remedied, such as the significant worsening of pain beyond the baseline.
- The progression of cardiac involvement.
- The new presentation of clinically significant neurovascular disease.

**Role of, and interactions with, the Lysosomal Storage Disease Medical Advisory Board**

The Lysosomal Storage Disease Medical Advisory Board is a multidisciplinary and multispeciality team of physicians with an interest in treating patients with LSD. This approach is essential, owing to the multisystem nature of the disorder. The physicians are also drawn from academic and private healthcare institutions. The members are independent, and aim to provide a shared-care model to enable treating physicians and funders to obtain advice on various aspects of the care of AFD patients. The intention is not to regulate care, but to improve patients’ care, through sharing knowledge and experience. These guidelines provide a standard of care that is in keeping with that internationally, but is also realistic for South Africa. It is the intention that all AFD patients should be identified, and offered the best possible available care, based on these guidelines.

**Interaction between treating physicians and the Lysosomal Storage Disease Medical Advisory Board**

The Lysosomal Storage Disease Medical Advisory Board will act as a consultant to assist treating physicians in the management and care of their patients.

**Interaction between medical aids and the Lysosomal Storage Disease Medical Advisory Board**

Medical aids and/or funders may consult the Lysosomal Storage Disease Medical Advisory Board with regard to patients who are new to treatment, or when dosage adjustments are requested.

Here is a list of the Lysosomal Storage Disease Medical Advisory Board members, in alphabetical order:

- Dr Louisa Bhengu, Medical Geneticist, University of the Witwatersrand.
- Prof Alan Davidson, Paediatric Haematologist, University of Cape Town.
- Dr Carla Els, Paediatric Pulmonologist, Private Practice.
- Dr Paul du Toit, Physician, Private Practice.
- Dr Trevor Gerntholtz, Nephrologist, Private Practice.
- Dr Kenny Govendragaloo, Paediatric Cardiologist, Private Practice.
- Dr Rene Heitner, Paediatrician, Private Practice, deceased.
- Dr Bertram Henderson, Medical Geneticist, University of the Free State.
- Dr Lawrence Mubaiwa, Paediatric Neurologist, University of KwaZulu-Natal.
- Dr Sheeba Verughese, Paediatrician, University of the Witwatersrand.
Disclaimer

These guidelines have been prepared for physicians and other healthcare professionals on behalf of the Lysosomal Storage Disorder Medical Advisory Board, and reflect the best available data at the time that the report was prepared. Caution should be exercised when interpreting the data. Alterations to the conclusions or recommendations in this report may be required following the results of future studies. It may be necessary, or even desirable, to depart from the guidelines in the interests of specific patients and special circumstances. These guidelines do not represent all the possible methods of management applicable to all patients, do not exclude any other reasonable methods and will not ensure successful treatment in every situation. The unique circumstances of each patient should be taken into account by the responsible physician making decisions on any specific therapy. Just as adherence to these guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

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Declaration

The meetings of the Lysosomal Storage Disorder Medical Advisory Board were sponsored by Genzyme Corporation, USA.

Conflict of interest

The Lysosomal Storage Disorder Medical Advisory Board is sponsored by Genzyme Corporation, USA.

References