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

Bhengu L, MBChB, FCP(SA), CertMedGenetics(SA), Medical Geneticist, University of the Witwatersrand
Davidson A, MBChB, FCPaed, CertMedOnc(Paeds), MPhil, Associate Professor and Head
Haematology Oncology Service, Red Cross War Memorial Children's Hospital, University of Cape Town
Du Toit P, BM, MMed(Int), Clinical Haematologist, Private Practice
Henderson B, MBChB, DCH, MMed Paeds, Head of Clinical Unit and Senior Lecturer
Division Human Genetics, Department of Neurology, University of the Free State; Universitas Hospital
Gerntholtz T, MBChB, FCP(SA), Nephrologist, Private Practice
Govendrageloo K, MBChB, MMed(Paeds), Paediatric Cardiologist, Private Practice
Heitner R, deceased; **Mubaiwa L,** MBChB, FCPaed(SA), MA(Child Dev), Paediatric Neurologist
Division of Paediatric Neurology and Child Development, University of KwaZulu-Natal
Varughese S, MBChB, FCPaed, Senior Specialist Paediatrician
Department of Paediatrics, Gaucher and HIV Clinic, Charlotte Maxeke Johannesburg Academic Hospital; University of the Witwatersrand
Correspondence to: Bertram Henderson, e-mail: gnmgbdh@ufs.ac.za
Keywords: Fabry disease, Anderson-Fabry disease, lysosomal storage disorder, enzyme replacement therapy (ERT), South Africa

Abstract

Background: Anderson-Fabry disease (AFD) is a rare, X-linked lysosomal storage disorder that leads to the accumulation of globotriasylceramide in the lysosomes in tissues throughout the body. The responsible gene is α-galactosidase A, found at chromosome Xq22. More than 400 mutations have been identified. The disease usually presents in childhood, is progressive and multisystem, and results in increasing disability and premature death.

Objective: The objectives of these guidelines are to provide a standard of care for patients with AFD that is in keeping with that internationally, but which is also realistic for South Africa, and to provide a shared-care model for treating physicians and funders with regard to various aspects of care for these patients.

Recommendations: All heathcare professionals involved in the diagnosis and management of AFD should take note of these guidelines and try to implement them in clinical practice as far as possible.

Validation: These guidelines were developed through general consensus by the Lysosomal Storage Disorder Medical Advisory Board, and are largely based on the UK 2005 national guidelines for AFD, but have also been updated to include new treatment recommendations for enzyme replacement therapy based on evidence from subsequent publications.

Conclusion: It is the intention that these guidelines will benefit all patients suffering from AFD disease, and enable them to be diagnosed and offered the best possible available care.

Ⓟ **Peer reviewed. (Submitted: 2014-11-20. Accepted: 2015-02-04.)** **JEMDSA 2015;20(1):15-23**

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,[1] 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.[1] AFD is the second most common of the 40 LSDs, after Gaucher's disease, with an incidence of 1:117 000 in Australia[2] and 1:468 000 in the Netherlands.[3] It occurs in all population and racial groups.[1]

The gene for α-gal A is located at chromosome *Xq22*, and more than 400 mutations have been identified.[1,4] The mutations are usually "private" (restricted to a single or few families) and commonly lead to complete lack of detectable enzymes.[1,4,5] The inheritance of AFD follows an X-linked pattern.[1] Hemizygous males carry a defective gene on the X chromosome and develop classical AFD.[1] 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.[1] However, a number of studies have demonstrated a significant burden of disease in females.[1,4]

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.[1,6] Earliest manifestations appear around age 10 years in males and several years later in females.[1,7] 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.[7,8]

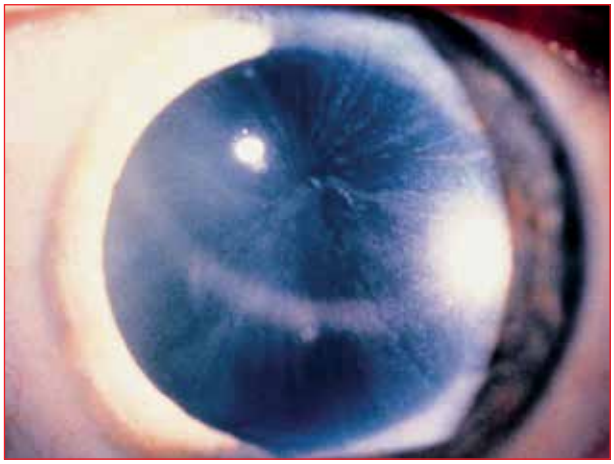
Early renal manifestations may include microalbuminuria and proteinuria. Further disease progression results in declining glomerular filtration rate (GFR), interstitial scarring, glomerulosclerosis, tubular atrophy, and ultimately end-stage renal disease.[7] Cardiovascular symptoms may include sinus node dysfunction, conduction abnormalities and arrhythmia, left ventricular hypertrophy, valvular dysfunction, angina pectoris, myocardial infarction and heart failure.[7] Cerebrovascular involvement can result in disturbed concentration, dizziness, dementia, headaches and learning difficulties,[9] an early stroke and/or transient ischaemic attack (TIA), as well as thrombosis or cerebrovascular haemorrhages.[1,7,9,10] Respiratory symptoms, such as dyspnoea and significant airflow obstruction, have been described in up to 61% of patients with the classical form of AFD.[1,4] 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.[11]

Although clinically variable, classical AFD is usually a progressive disease, in which the signs and symptoms change as the patient ages.[1,7] 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.[1,9,12]

Clinical features

Childhood and adolescence (≤ 16 years)

The most common clinical features are acroparaesthesiae, pain and AFD "crises" in childhood and adolescence.[1] 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 anhydrosis, 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.[1] Oedema, fever, hypohidrosis 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.[1]

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 transplantation[4,7,18] 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 m^2 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" variant[19] 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.[9] 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

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.[7] 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.[1,7]

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.[1] Adjunctive therapies include the treatment of pain, hypertension, renal disease, cardiac disease, CNS involvement and

Table I: Differential diagnoses of Anderson-Fabry disease

Features of Anderson-Fabry disease	Misdiagnosis
Angiokeratoma	Petechiae of meningococcal meningitis, hereditary haemorrhagic telangiectasia, Fordyce disease, Schindler disease, fucidosis and sialidosis
Pain	Rheumatoid arthritis, rheumatic fever, Raynaud's disease and "growing pains"
Neurological symptoms	Multiple sclerosis
Renal impairment	Glomerulonephritis, pyelonephritis and exposure to silica dust
Cardiac involvement	Hypertrophic or restrictive cardiomyopathy, congestive cardiac failure and coronary artery disease
Gastrointestinal symptoms	Irritable bowel syndrome and pancreatic insufficiency
Cornea verticillata	Amiodarone or chloroquine therapy

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

System	Investigation	Initial evaluation	Frequency at follow up
General	Medical and general history	X	6 monthly
	Family pedigree	X	
	History of concomitant medications		Each infusion
	Clinical examination	X	3 monthly
	Vital signs	X	Each infusion
	Pain score (PBI)	X	12 monthly
	Quality of life score (age appropriate), i.e. SF-36 or EQ5D	X	12 monthly
	Mainz Severity Score Index[21]	X	12 monthly
	Adverse event recording		Each infusion
Cardiac	ECG	X	12 monthly
	24-hour ECG	X	As clinically indicated
	Echocardiogram	X	As clinically indicated, annually after age 35 years
	Symptom-limiting exercise testing	If clinically indicated	
Renal	GFR	X	12 monthly, or as indicated
	Spot urine albumin and creatinine ratio (first morning void)	X	12 monthly
	Spot serum creatinine (morning)	X	12 monthly
	Renal biopsy	At the discretion of the nephrologist	

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

α-gal A: **α-galactosidase A**, ECG: electrocardiogram, eGFR: estimated glomerular filtration rate, EMG: electromyography, EQ5D: EuroQOL five dimensions questionnaire, ERT: enzyme replacement therapy, GFR: glomerular filtration rate, GL3: globotriaosylceramide, MRI: magnetic resonance imaging, PBI: Present Behavioural Intensity, SF-36: Short-Form 36 item health status survey

Table III: Adjunctive therapies in Anderson-Fabry disease

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

ACE: angiotensin-converting enzyme, TIA: transient ischaemic attack

angiokeratoma, and should be available to all patients who are symptomatic.[7] 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.[1]

Table IV: Indications for enzyme replacement therapy

General symptoms of Anderson-Fabry disease	
Evidence of renal disease	Pain interfering with quality of life
	GFR (< 80 ml/minute)
	Microalbuminuria
	Proteinuria of > 300 mg/24 hours
	Renal biopsy showing endothelial deposits
Evidence of cardiac disease	Left ventricular hypertrophy on ECG
	Conduction abnormalities
	Increased left ventricular mass on echo
	Increased left ventricular wall thickness on echo
	Left atrial enlargement
	Valvular thickening and insufficiency
	A reduction in left ventricular ejection fraction
	Diastolic dysfunction
	Ischaemic heart disease in the absence of coronary artery disease
Evidence of neurovascular disease	A previous stroke or TIA
	The progression of abnormal cerebral MRI scans
Gastrointestinal symptoms	Symptoms significantly altering quality of life
The following are indications for ERT in boys:	
ENT	Hearing loss
	Episodic vertigo
General	Poor growth that is unexplained
	Significant symptoms affecting quality of life
Renal	Proteinuria or microalbuminuria
The following are indications for ERT in women:	
General	Proteinuria or microalbuminuria
	Acroparasthesia non-responsive to conventional treatment
	Persistent proteinuria of ≥ 300 mg/24 hours
	GFR below 80 ml/minute/1.72 m^2
	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

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

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 paraesthaesia. 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.[27] 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,[1] actions to be considered include 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:[1]

- 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.

Acknowledgements

The contributions of the following Lysosomal Storage Disorder Medical Advisory Board members are gratefully acknowledged: Dr Louisa Bhengu, Prof Alan Davidson, Dr Paul du Toit, Dr Trevor Gerntholtz, Dr Kenny Govendrageloo, Dr Rene Heitner, Dr Bertram Henderson, Dr Lawrence Mubaiwa and Dr Sheeba Varughese. The authors are indebted to Southern African Society for Human Genetics members for their constructive comments on this document and their willingness to endorse it.

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

1. Hughes DA, Ramaswami U, Elliot P, et al. UK 2005 NCG guidelines for the diagnosis and management of Anderson-Fabry Disease. National Health Service [homepage on the Internet]. c2011. Available from: http://www.specialisedservices.nhs.uk/library/23/Guidelines_for_Anderson_Fabry_Disease.pdf
2. Meikle PJ, Hopwood JJ, Clague AE, et al. Prevalence of lysosomal storage disorders. JAMA. 1999;281(3):249-254.
3. Poorthuis BJHM, Wevers RA, Kleijer WJ, et al. The frequency of lysosomal storage diseases in the Netherlands. Hum Genet. 1999;105(1-2):151-156.
4. Martins AM, D'Almeida V, Kyosen SO, et al. Guidelines to diagnosis and monitoring of Fabry disease and review of treatment experiences. J Pediatrics. 2009;155(4 Suppl 2):S19-S31.
5. Beck M, Ricci R, Widmer U, et al. Fabry disease: overall effects of agalsidase alfa treatment. Eur J Clin Invest. 2004;34(12):838-844.
6. Peters FPJ, Vermeulen A, Kho TL. Anderson-Fabry's disease: □-galactosidase deficiency. Lancet. 2001;357(9250):138-140.
7. Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med. 2006;8(9):539-548.
8. Ries M, Ramaswami U, Parini R, et al. The early clinical phenotype of Fabry disease: a study of 35 European children. Eur J Pediatr. 2003;162(11):767-772.
9. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. J Med Genet. 2001;38(11):750-760.
10. Mitsias P, Levine SR. Cerebrovascular complications of Fabry's disease. Ann Neurol. 1996;40(1):8-17.
11. Cole AL, Lee PJ, Hughes DA, et al. Depression in adults with Fabry disease: a common and under-diagnosed problem. J Inherit Metab Dis. 2007;30(6):943-951.
12. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females (letter). J Med Genet. 2001;38(11):769-775.
13. Nakao S, Takenaka T, Maeda M, et al. An atypical varient of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med. 1995;333(5):288-293.
14. Cable W JL, Kolodny E H, Adams RD. Fabry disease: impaired autonomic function. Neurology. 1982;32(5):498-502.
15. Sher NA, Letson RD, Desnick RJ. The ocular manifestations of Fabry's disease. Arch Ophthalmol. 1979;97(4):671-676.
16. Hajioff D, Enever Y, Quiney Y, et al. Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. J Inherit Metab Dis. 2003;26(8):787-794.
17. Moller AT, Jensen TS. Neurological manifestations in Fabry's disease. Nature Clin Pract Neurol. 2007;3(2):95-106.
18. Tsakiris D, Simpson HKL, Jones EHP, et al. Rare diseases in renal replacement therapy in the ERA-EDTA Registry. Nephrol Dial Transplant. 1996;11 Suppl 7:4-20.
19. Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation. 2002;105(12):1407-1411.
20. Clarke LA, Clarke JTR, Sirrs S, et al. Fabry disease: Recommendations for diagnosis, management and enzyme replacement therapy in Canada. The Garrod Association [homepage on the Internet]. 2005. c2011. Available from: http://www.garrod.ca/data/attachments/CanadianFabryGuidelinesNov05.pdf
21. Whybra C, Kampmann C, Krummenauer F, et al. The Mainz Severity Score Index: a new instrument for quantifying the Anderson–Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clin Genet. 2004;65(4):299-307.
22. Schiffman R, Kopp JB, Austin AH 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomised controlled trial. JAMA. 2001;285(21):2743-2749.
23. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human α-galactosidase A replacement in Fabry disease. N Engl J Med. 2001;345(1):9-16.
24. Hughes DA, Deegan PB, Milligan A, et al. A randomised, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of three dosing schedules of agalsidase alfa enzyme replacement therapy for Fabry disease. Mol Genet Metab. 2013;109(3):269-275.
25. Hughes DA, Elliott PM, Shah J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart. 2008;94(2):153-158.
26. El Dib RP, Nascimento P, Pastores GM. Enzyme replacement therapy for Anderson-Fabry disease. [Cochrane Review]. In: The Cochrane Library, Issue 2, 2013. Oxford: Update Software.
27. Vedder AC, Linthorst GE, Houge G, et al. Treatment of Fabry disease: outcome of a comparative trial with Agalsidase alfa or beta at a dose of 0.2 mg/kg. PLoS One. 2007;2(7):e598.
28. Linthorst GE, Vedder AC, Oremel EE, et al. Home treatment for Fabry disease: practice guidelines based on three years experience in The Netherlands. Nephrol Dial Transplant. 2006;21(2):355-360.
29. Banikazemi MM, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med. 2007;146(2):77-86.