

Adult Fabry Disease Standard Operating Procedures

These standard operating procedures (SOPs) have been prepared in 2012 (to assist commissioning of services for Adult Fabry Disease in England) by a group of prescribing physicians working in designated treatment centres at the invitation of the National Specialist Commissioning team. The SOP is designed to regulate practice in England and is not a clinical guideline for use elsewhere. Physicians and commissioners have examined the clinical evidence in the context of the cost of treatment as it pertains to the healthcare system in England.

Document controller: Dr Derralynn Hughes rmgvdah@ucl.ac.uk

Last update: January 2013

Membership of the LSD Expert Advisory Group (January 2013)

Mr Dan Brown

Dr Anupam Chakrapani

Dr Maureen Cleary

Ms Tanya Collin-Histed

Prof Tim Cox

Dr Charlotte Dawson

Dr Patrick Deegan

Dr Chris Hendriksz

Dr Tarek Hiwot

Dr Derralyynn Hughes

Dr Simon Jones

Dr Ana Jovanovic

Dr Edmund Jessop

Dr Robin Lachmann

Mrs Christine Lavery

Ms Toni Matheson

Prof Atul Mehta

Mr Allan Muir

Dr Elaine Murphy

Dr Uma Ramaswami

Dr Reena Sharma

Ms Sheela Upadhyaya

Dr Ashok Vellodi

Dr Suresh Vijay

Prof Ed Wraith

ABSTRACT

Anderson-Fabry disease (AFD) is a rare, X-linked lysosomal storage disorder that leads to accumulation of globotriasylceramide throughout the body. The disease usually presents in childhood, is progressive and results in increasing disability and premature death. Males and females can be affected although the disease in females is usually milder and of later onset. Treatment used to be entirely symptomatic, but the advent of enzyme replacement therapy has made it necessary to have explicit guidelines for the diagnosis, assessment, treatment and follow up of patients and families.

Contents

1.0 Anderson-Fabry Disease: an overview

2.0 Baseline Assessment at Diagnosis, Presentation or commencement of Therapy

3.0 Treatment of Anderson-Fabry Disease

4.0 Follow-up

APPENDIX 1

Fabry Disease: Paediatric Patients

2.01.0 Anderson-Fabry Disease: an overview

Anderson-Fabry disease (AFD)—also known as Fabry disease is a rare, X-linked lysosomal storage disorder (LSD), caused by an inborn deficiency of α -galactosidase A (α -Gal A). The resulting inability to catabolise glycosphingolipids causes progressive accumulation of globotriaosylceramide (CTH) in endothelial cells, vascular smooth muscle, erector pilori muscles in the skin, myocardium, corneal epithelial cells and in organs such as the kidney, pancreas, bowel and lung (Peters et al 2001). The resulting symptoms usually appear during childhood and adolescence (Ries et al 2003), affect many organ systems and may lead to progressive disease and premature death.

AFD is the second commonest of the 40 LSDs (after Gaucher disease), with an incidence of one in 117,000 in Australia (Meikle et al 1999) and one in 476,000 in the Netherlands (Poorthuis et al 1999) and occurs in all racial groups. More recently, however, a screening study of new born males in Italy has suggested that the incidence may be as high as 1:3100 (Spada et al). Milder, atypical AFD with symptoms confined to one organ may be more common (see below).

The gene for α galactosidase A is on Xq22 and more than 350 mutations have been identified (Desnick et al. 2001; Schafer et al 2004). Most are small deletions or insertions and numerous single based substitutions leading to missense or nonsense mutations. The mutations are usually 'private' (restricted to a single or few families) and usually lead to complete lack of detectable enzyme in males (Garmon & Garboczi, 2004). The diagnosis is often missed (Morgan & d'A Crawford, 1988; Mehta, Lewis & Lavery, 2002); in UK males it takes a mean of 8.18 years from onset of neuropathic pain and a mean of 10.70 years from the onset of angiokeratoma.

The inheritance of AFD follows an X-linked pattern. Hemizygous males carry a defective X-chromosome and develop classical AFD. Heterozygous females have one normal and one abnormal X chromosome; they usually have

disease which has later onset than hemizygous males. However, a number of studies have demonstrated a significant burden of disease in females (MacDermott et al 2001; Whybra et al 2001, Deegan et al 2006). Indeed, all the manifestations described in males may also occur in females, though typically the disease has a later onset, slower progression and less severe clinico-pathological changes.

1.1 Clinical Features

Although clinically heterogenous, classical AFD is usually a slowly progressive disease in which signs and symptoms change as the patient ages (Mehta et al, 2004). The main causes of death are renal failure, heart disease or stroke around the age of 50 years for hemizygous men (MacDermott et al 2001 [a]) and 70 years for obligate carrier women (MacDermott et al 2001 [b]).

Disease progression in AFD

Childhood and adolescence (≤16- years)

- Acroparaesthesiae Pain and AFD crises
- Angiokeratomas
- Ophthalmological abnormalities, especially cornea verticillata
- Hearing impairment
- Dyshydrosis (hypohydrosis and hyperhydrosis)
- Non specific bowel disturbances
- Lethargy and tiredness

Early adulthood (17 – 30 years)

- More extensive angiokeratomas
- Proteinuria, lipiduria, haematuria
- Oedema
- Fever
- Hypo- or anhidrosis
- Heat sensitivity

- Diarrhoea, abdominal pain

Later adulthood (age > 30 years)

- Cardiac involvement (see later)
- Impaired renal function
- Stroke or TIA

1.2 Diagnosis

It is common for Anderson-Fabry Disease to be misdiagnosed as the differential diagnosis of many of the associated clinical features is wide. It is important that diagnosis is confirmed in all newly presenting patients including those presenting in the context of family screening. In males the diagnosis may be confirmed by enzymatic analysis of leucocyte or plasma alpha galactosidase A and/or DNA analysis of the alpha galactosidase A gene. In women genotyping is essential as enzymatic levels of the female heterozygote may lie within the normal range. In cases where DNA analysis is non-conclusive examination of urine for CTH and cornea for verticillata may assist in the diagnosis.

A diagnosis of Fabry disease is only confirmed where a mutation previously documented as causing relevant pathology is identified. If a new mutation/sequence variant is identified this should be accompanied by biochemical evidence of decreased enzyme activity in males (decreased in expression systems in females) and evidence of substrate accumulation in urine or on biopsy.

Family Screening

Pedigree analysis should be made of each patient presenting with Anderson-Fabry disease. This should be done by physicians and nurses with training and experience in genetic counselling. Access to regional genetic services should be available. Written informed consent should be obtained prior to any genetic test and support and counselling should be available at each stage. Confidentiality

between family members should be maintained at all times and permission of the GP should be sought prior to testing/investigating any individual.

1.3 Treatment

Two enzyme formulations are licensed in Europe for the treatment of AFD: agalsidase alfa (Replagal™, Shire HGT) at a dose of 0.2mg/kg intravenously every two weeks and agalsidase beta (Fabrazyme™, Genzyme Corporation). at a dose of 1mg/kg intravenously every two weeks. Agalsidase beta was approved by the FDA in the USA in 2003. Agalsidase alfa is produced using a genetically engineered human fibroblast cell line. Agalsidase beta is produced using a Chinese hamster ovary cell line. The product licences are based on the National Institute of Health (NIH) study using agalsidase alfa (Schiffman et al 2001) and the trial using agalsidase beta conducted by the Mount Sinai School of Medicine study group (MSSG) (Eng et al 2001). Both studies were randomised, double-blind and placebo-controlled, but differed in details of their entry criteria and outcome measures. The NIH study recruited 28 men aged over 18 years with neuropathic pain; the MSSG study included 56 men and two women aged over 16 years with serum creatinine ≤ 2.2 mg/dl (194.5 μ mol/L). The actively treated group in the NIH study (14 men, mean age 34.0) were older and had more clinically measurable disease than in the MSSG study (27 men and 2 women, mean age 32.0). The randomised phases of studies were approximately equal —24 weeks (NIH study) and 20 weeks (MSSG study) —followed in both studies by 24 weeks open-label treatment and an extension phase. These trials have shown both preparations to be broadly equivalent in the doses used as measured by laboratory assessment of treated versus placebo groups (eg. statistically significant reductions in urine and plasma CTH content, renal histology).

The NIH group has subsequently reported that agalsidase alfa treatment has resulted in significant reduction in abnormal cerebral perfusion and the resolution

of abnormally increased cerebrovascular blood flow (Moore et al 2001 [a]; Moore et al 2001 [b]; Moore et al 2002). Treatment with agalsidase alfa has also been shown to stabilise renal function, cardiac abnormalities and pain (Beck et al, 2004); to improve quality of life (Hoffman et al 2004) and to improve hearing (Hajioff et al, 2002). Treatment with agalsidase beta has been shown to improve or stabilise or improve cardiac function (Waldek et al) and renal function (Germain et al 2007). A recently completed phase IV randomised double blind trial of agalsidase beta shows a reduction in clinical progression of the disease in treated patients with respect to renal, cardiac and CNS events (Banikazemi et al 2007).

The safety of enzyme replacement therapy in young children has been recently demonstrated in two clinical trials. A clinical trial of Replagal in children aged 2 to 18 years was performed. Safety and efficacy of enzyme replacement therapy with agalsidase alfa, 0.2 mg/kg infused over 40 minutes every 2 weeks for 23 weeks, were studied in a multicentre open-label trial in nine boys and four girls. Median age at the start of the study was 11.0 years (range, 3.5–18 years).: Fifty-four adverse events were reported in 11 patients. No serious adverse events related to enzyme replacement therapy were reported. Twelve of the 54 adverse events were considered possibly or probably related to enzyme replacement therapy. Infusion reactions (8 mild, 3 moderate) occurred in four boys, in seven infusions. One boy developed IgG antibodies, although he continued to make good clinical progress. At the end of the study, two of the four boys and the one girl on regular pain medication at baseline had stopped taking analgesics. Brief Pain Inventory (BPI) scores decreased in most patients by week 12 and were sustained until the end of the study. This change was greater in the boys, who had higher (worse) BPI scores at baseline. Pain-related quality of life scores also

decreased during the study. Plasma globotriaosylceramide concentrations and urinary globotriaosylceramide: sphingomyelin ratios decreased after 12 and 23 weeks of therapy, particularly in the boys. Increases in sweat volume were recorded in three out of five of the boys and in one of two girls tested after 23 weeks of treatment. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease is well tolerated and, in the short term, appears to decrease pain and to improve pain-related quality of life (Ramaswami et al. 2007).

In the second international, open-label study, children with AFD were treated with 1.0 mg/kg Fabrazyme biweekly. A total of 16 symptomatic children (14 males, 2 females) with a mean age of 12.1 years (range 8 to 16 years) were enrolled. The patients were first observed for a period of 12 weeks, and then treated for a period of 48 weeks. Treatment was generally well tolerated, and the adverse events reported consisted mainly of headache, pain, abdominal pain, fever, rhinitis, rigors and nausea. In addition, one serious adverse event related to study treatment was reported; the patient recovered quickly but treatment was discontinued. Histological evaluation of the capillary endothelium (vasculature) in the skin, for CTH accumulation, was conducted using light microscopy at Baseline and Week 24. All samples were scored by a group of 3 independent pathologists in a blinded manner, according to a none-mild-moderate-severe scale (0-1-2-3). At Baseline, 11 of 15 patients (including the 2 youngest) presented a moderate GL-3 accumulation (i.e., a score of 2). None of the 2 females presented a detectable accumulation at Baseline. For one male patient the result is pending. After 24 weeks of treatment, all 16 patients showed a score of 0 in the skin. Plasma CTH levels, measured by mass spectrometry, were abnormal at Baseline for all males (but not for the 2 females) and normalised (i.e., < 7.03 µg/mL) after 24 weeks of treatment. (Wraith et al 2008).

ERT seems to be well tolerated by patients with AFD. Antibody function has

been reported with both preparations but there is no clear evidence of any impact on clinical efficacy of treatment (Linthorst et al, 2004). For the purposes of these guidelines it is assumed that both preparations will be available for prescription and patients will be offered a choice of products.

Evidence for treatment effect on clinical manifestation of AFD

Level of evidence for improvement is presented in bold.

Cardiac	LVH- 1b/A , (Macdermott 2007) Conduction abnormalities- 1b/A (,Waldek, 2003) Cardiac Endothelium CTH 1b/A (Eng 2001) Systolic/diastolic dysfunction IIa/B (Weidemann 2003)
Renal	Urine CTH- 1b/A (Eng 2001 Schiffman 2001) Renal CTH- 1b/A (Eng 2001,Schiffman 2001) Proteinuria Reduced GFR/CrCl- 1b/A (Schiffman 2001)
Neurovascular	Dermal CTH- 1b/A (Eng 2001) Hearing impairment- 1b/A (Hajioff 2003) Pain- 1b/A (Schiffman 2001) Neuropathy- IIa/B (Hiltz, 2004)
Gastrointestinal	GI symptoms- IIb/B (Dehout 2004)
Quality of Life	Reduced EQ5D/ SF36- 1b/A (Eng 2001, Schiffman 2001)

1,4 Principles of treatment and assessment of response

Appropriate setting for the management of Anderson Fabry Disease

An experienced consultant, who is part of an approved NCG designated centre in accordance with UK NHS strategy, should supervise the treatment of

patients with Anderson-Fabry Disease. Effective and high-quality care requires a multi-speciality and multi-disciplinary team familiar with the range of clinical problems likely to be encountered. The following represent the core range of essential accessible expertise and services, which may be available at the treatment centre or in a neighbouring hospital. There should be clear policies and protocols for access to these services.

- Nurse specialists
- Clinical pathology
- Clinical Genetics
- Paediatrician with expertise in Fabry Disease
- Radiology
- Cardiology
- Neurology
- Dermatology
- Ophthalmology
- Audiology
- Pharmacy facilities and expertise
- Renal service, including rapid access to haemodialysis. (Patients with renal failure should be managed jointly with a renal physician)
- Primary care liaison
- Palliative care physicians/nurses
- Physiotherapy/rehabilitation
- Administrative support for case registration, audit and clinical trials
- Social services and financial advice
- Patient support group (possibly through national organizations)

2.0 Baseline Assessment at Diagnosis, Presentation or commencement of therapy:

Once a diagnosis is confirmed the aim of further investigations is to provide a precise assessment of the severity of the clinical manifestations of the disease in the patient. This will further allow the requirement for

specific and adjunctive therapies to be considered and will provide the baseline against which the effectiveness of such therapies will be assessed.

Recommended Investigations for patients with Anderson-Fabry disease

General:

1. Medical history and family pedigree
2. Clinical examination
3. Vital signs
4. Pain score (BPI)
5. Age appropriate Quality of Life score (SF-36 or EQ5D), Fabry Specific paediatric health related questionnaire (this is only in FOS at present)
6. Severity Score Index for adults– MSSI (Whybra et al 2004)

Cardiac:

1. ECG
2. 24 hour ECG
3. Echocardiogram
4. Symptom limiting exercise testing / vmAX to be considered in selected adults eg those with exercise-induced arrhythmia

Renal:

1. Glomerular Filtration Rate: Cr51 EDTA OR estimated GFR (mdrd). Conahan-Barratt method for patients less than 16 years of age.
2. If (1) is not available the 24 hour urine Cr Clearance may be performed
3. 24 Hour urine protein (in children over 10 years if appropriate)
4. Spot urine Alb/Creatinine ratio or protein/Creatinine ratio (this is what we do routinely). For children aim to perform three consecutive early morning urine samples
5. Renal biopsy- at the discretion of the renal physician
6. Renal USS

Neurology

1. T2 weighted MRI brain examination (CT if MRI precluded by pacemaker etc).
In children if clinically indicated or does not require a general anaesthetic.

Ophthalmology:

1. Slit-lamp examination (cornea verticillata)
2. Retroillumination (AFD cataract)
3. Retinal examination (vascular abnormalities)

Audiology:

1. Pure tone audiogram or age appropriate hearing assessments
2. Vestibular examination

Laboratory Investigations:

1. Full blood count
2. Urea & electrolytes and creatinine
3. Liver function tests
4. Fasting lipid profile (not in children)
5. Plasma CTH where available

Urine

1. Urine CTH (10 mls of urine in a universal container sent either immediately or frozen as for blood above)

3.0 Treatment of Anderson-Fabry Disease

Therapy of Anderson-Fabry Disease comprises both specific replacement of the deficient alpha-galactosidase A (enzyme replacement therapy) and supportive or adjunctive therapy of complications of the condition. Adjunctive therapies include treatment of pain, hypertension and angiokeratoma and should be available to all patients who are symptomatic. There are no randomised controlled trials of these therapies in Anderson Fabry Disease and the evidence for their effectiveness is largely derived from experience in other conditions and is therefore Grade C evidence level IV.

3.1 Adjunctive treatment

Pain

Chronic pain: anticonvulsants (eg carbamazepine, gabapentin)

AFD crises or when necessary: strong analgesia including opiates,

Minimisation of activities that trigger painful crises eg physical exertion, temperature changes, emotional stress

Angiokeratoma

Removal (if desired by the patient) with argon laser therapy

Renal disease

Early stages of impairment:

ACE inhibitors or Angiotensin receptor 2 blockers when proteinuria exceeds 300mg/24 hour (in patients without renal artery stenosis)

Renal failure: dialysis or transplantation

Cardiovascular disease

Chest pain: anti-anginals (calcium antagonists, nitrates)

Heart failure: Diuretics, ACE inhibitors, digoxin,

Atrial ventricular tachycarrhythmia: antiarrhythmics, anticoagulants, ICDs

(<http://www.nice.org.uk/Guidance/TA11>)

Symptomatic bradycardia: pacemaker

Hypertension Rigorous control eg ACE inhibitors. Avoid beta blockers where sinus bradycardia

Hyperlipidaemia is common in patients with Anderson-Fabry disease: it should be treated according to local/national guidelines

Gastrointestinal symptoms

Low-fat diet, small and frequent meals, motility agents

Neurovascular Disease

Aspirin, clopidogrel

3.2 Enzyme replacement therapy

A number of randomised controlled trials have investigated the therapeutic effect of recombinant alpha galactosidase A on the clinical manifestations of Anderson Fabry Disease providing evidence at level 1b and recommendation grade A (Eng, 2001, Schiffman 2001). No trial has yet addressed the appropriate starting time of treatment or the group of patients most likely to benefit from therapy.

However this is a chronic, progressive disorder. The aim of treatment is to prevent progression and where disease is already manifest to try and reverse or stabilise the disease. It is anticipated that treatment will be most successful when started early in the course of the disease. Conversely treatment late in the course of the disease may have limited efficacy

The manifestations responsive to ERT have been used to devise criteria for initiating therapy.

Starting Criteria

In males with 'classical mutations (leucocyte enzyme activity <1%) enzyme replacement therapy should commence at diagnosis. In females and those males with 'later onset' mutations with higher levels of leucocyte enzyme activity enzyme replacement therapy should commence when one of the following criteria are fulfilled. (An appendic of mutations is in preparation)

1. General symptoms of Anderson-Fabry disease, specifically

-Uncontrolled pain leading to a need to alter lifestyle or pain that interferes with quality of life * Pain is often a first manifestation of the disease and therapy started at this stage is also intended to arrest progression to involvement of other organ systems.

2. Evidence of renal disease

- a. Clinically significant reduction in Glomerular Filtration Rate (< 80 ml/min adjusted according to age)
- b. In males Proteinuria >300 mgs/24 hours.
- c. In males Microalbuminuria where a renal biopsy showed endothelial deposits, vascular or interstitial changes
- d. In children: persistent microalbuminuria (three consecutive early morning urine samples or 3 early morning urine samples over a period of one month).

3. Evidence of cardiac disease

A. ECG

- a. presence of left ventricular hypertrophy (Romhilt-Estes or Cornell criteria)
- b, Isolated repolarisation abnormalities (in absence of other causes such as hypertension, aortic stenosis)
- c. Conduction abnormalities: (Short PR interval, 1, 2 or 3 degree heart

block, bundle branch block)

B. Echocardiogram

a .Increased left ventricular mass (in patients with concentric remodelling or hypertrophy) Criteria (Devereux et al 1977,1986)

Normal LVMI defined as $< 134 \text{ gm/m}^2$ for men and $< 110 \text{ gm/m}^2$ in females.

Relative wall thickness (RWT) calculated as $((\text{IVS} + \text{PW})/\text{LVed})$ at the mitral valve level.

LV remodelling or LVH defined as a $\text{RWT} > 0.4514$.

LV geometry defined as normal (normal LV mass and normal RWT), concentric remodelling (normal LV mass and increased RWT), eccentric LVH (increased LV mass and normal RWT), and concentric LVH (increased LV mass and increased RWT).

b. Increased left ventricular wall thickness (13 mm in any segment).

c. Left atrial enlargement

d. Valvular thickening/insufficiency

e. Systolic impairment (regional wall motion abnormality or reduction in left ventricular ejection fraction ($< 50\%$))

f. Diastolic dysfunction (using age corrected Doppler assessment)

C. Arrhythmia

a.24 hour ECG (or other documented ECG evidence) showing bradyarrhythmia, atrial arrhythmia, ventricular tachycardia.

D. Ischaemic heart disease: positive exercise test, PET scan in the ABSENCE of angiographically significant epicardial coronary artery disease.

4. Evidence of Neurovascular disease

-Previous stroke or TIA in the absence of other risk factors

-Progression of abnormal cerebral MRI scans

5. Gastrointestinal symptoms such as pain, vomiting or altered bowel habit which are significantly reducing quality of life and not attributable to other

pathology.

Please see Appendix 1 for paediatric baseline assessments

Exclusion Criteria for Enzyme Replacement Therapy:

1. The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy.
2. Patients with Fabry disease who are deemed too severely affected to benefit from enzyme replacement therapy (Eg Severely incapacitated following stroke/ Dementia).
3. End stage renal failure requiring dialysis in the absence of other starting criteria
4. Severe cardiac fibrosis/ ICD/PM in the absence of other starting criteria

Delivery of Enzyme Replacement Therapy:

Patients will be offered either Replagal or Fabrazyme.

1. Replagal 0.2 mg/kg in 100 mls of saline over 40 minutes, or
2. Fabrazyme 1.0 mg/kg in 500 mls of saline over 4 hours, reducing to 90 minutes as tolerated.

Fabrazyme

There has been discussion about the prescription of Fabrazyme at doses lower than 1.0mg/kg. This has been termed “the licensed dose”. The strict requirements of the Medicines Act and the ABPI Code of Practice for the Pharmaceutical Industry are that promotion of products must be in accordance with the summary of product characteristics (SPC) which forms the wording of the marketing license for a product granted by the competent authority. The SPC for Fabrazyme describes dosing at both 1.0 mg/kg and at 0.3 mg/kg. Prescribing at these doses is therefore in accordance with the SPC for Fabrazyme and both doses are therefore “licensed” and may be prescribed

at the professional discretion of licensed medical practitioners in accordance with the SPC as appropriate to the clinical requirements of individual patients.

Pre-medication with paracetamol, chlorpheniramine, hydroxyzine or hydrocortisone will be given at the discretion of the prescribing clinician. The first 1-3 infusions idose 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 pre-medication as above. When the clinician is confident that infusions will proceed without serious or life-threatening reaction then patients may be offered home infusion therapy. This will be initiated by an accredited home care nursing service but ultimately, after appropriate training, enzyme may be administered by the patient himself.

Persistent reaction to enzyme infusion should be assessed by clinician and the existence of antibodies to alpha-galactosidase A investigated. In the case of anaphylactic-type reactions this should be treated as a medical emergency, infusions suspended and the existence of IgE antibodies immediately investigated.

4.0 Follow-up:

For patients receiving enzyme replacement therapy:

If patient are receiving shared care with a local centre then the responsibility for result interpretation, treatment decisions and dose adjustment will rest with the NCG-designated centre. Protocols for management of shared care patients should available.

At each infusion (unless patients self-administering enzyme at home):

1. Vital signs
2. Adverse events
3. Concomitant medications

Every 6 months:

1. Medical history and concomitant medications
2. Clinical examination
3. Vital signs
4. Pain score (BPI)
5. Quality of Life score (SF-36 or EQ5D)
6. Full blood count, urea & electrolytes, liver function, fasting lipid profile (12 monthly suffice for children unless they are on ERT)
8. Urine tests (Albumin/creatinine ratio, urine protein)
9. ECG (12 monthly unless they are on ERT)/

Every 12 months:

As at six months with the addition of:

1. GFR
2. 24 hour urinary protein: creatinine ratio or albumin: creatinine ratio.
(spot urine albumin/creatinine and protein/creatinine ratios in children as 3 consec early morning samples).
3. Echocardiogram
4. 24 hour ECG
5. MRI scan if abnormal at baseline (2 years if normal at baseline)
6. Audiology
7. Quality of Life score
8. Assay for alpha-galactosidase A antibodies.
9. Plasma and Urine CTH

NB: In children – GFR, 24 hour ECG, 24 hour urinary protein, and MRI brain will be performed depending on age of patient and, if co-operative. Please see Appendix 1 of baseline assessments for further details.

5.0 Efficacy end-points:

An improvement in or a prevention of deterioration in:

1. Renal function (defined by GFR or 24 hour urine creatine clearance or proteinuria)
2. Pain scores
3. Age appropriate Quality of Life measurement
4. Cardiac structure and function
5. Neurological status
6. Growth and development in Children
7. Composite endpoint using a severity score index if available

Actions to be considered if there has been no change in symptoms after 12 months therapy:

1. Increase the dose of enzyme as part of a clinical trial
2. Change to the alternative enzyme product
3. Stop treatment
4. Continue on same dose

Safety end-points:

Safety should be monitored by:

1. Clinical examination
2. Vital signs
3. Routine bloods

Adverse events:

Divide into infusion and non-infusion related and scored as mild, moderate or severe.

Indications for cessation of specific treatment

Specific treatment may be withdrawn under the following circumstances:

GENERAL:

1. Intolerable and unavoidable adverse effects.
2. Intercurrent illness, where either long-term quality of life or expected survival is such that the patient will gain no significant benefit from specific treatment for Fabry disease.
3. At the request of the patient, or properly allocated guardian acting in the patient's best interests, if the patient is properly deemed not competent.
4. 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.
5. If the health and wellbeing of medical and/or nursing staff are placed under significant threat as a result of the actions or lifestyle of the patient.
6. Emigration of the patient outside the jurisdiction of the UK, when administration and funding of the treatment becomes the responsibility of Health Services in the new country of residence / domicile.

SPECIFIC:

To be considered annually from the first anniversary of start of ERT

Objective evidence of progression in measured clinical criteria which are not

- (1) Attributable to a secondary pathology
- (2) Commensurate with natural age-related decline
- (3) Remediable by increasing dose, changing product or institution of other simple therapeutic measure.
- (4) Within the normal measured variation of that laboratory parameter.
- (5) Out weighed in clinical significance by stabilisation or improvement in one of the other criteria.

On the basis of current major criteria these might include:

- a. Worsening of pain beyond baseline
- b. Deterioration of GFR or proteinuria (?20% decline)
- c. Progressive impairment of systolic or diastolic dysfunction resulting in worsening heart failure symptoms
- d. New presentation of clinically significant neurovascular disease

Shared Care Protocol

The service supports the use of shared-care arrangements with physicians based closer to the patient's home. The principles and responsibilities of the shared care arrangements between Trusts should be outlined in Shared Care policy documents

Interaction between centres

All centres will undertake to give the patient the opportunity of a second medical opinion if requested. All centres will inform patients of their right to seek advice from another centre and from the MPS society.

Adult treatment centres will undertake to refer patients in the paediatric age group to a paediatric centre of the patient's and parents' choice. Paediatric centres will undertake to refer patients to the adult centre of their choice on reaching the age of 16-18. Adult and paediatric centres undertake to ensure as much as possible a seamless transfer of care.

Audit:

Each treatment centre should audit their service. This will include audit of service provision including patient satisfaction surveys and audit of treatment efficacy using the end points outlined above. Other audit activity will be national and based on input into the national registry when developed.

References

- Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, Desnick RJ; Fabry Disease Clinical Trial Study Group. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med.* 2007 Jan 16;146(2):77-86.
- Beck M, Ricci R, Widmer U, Dehout F, Garciade Lorenzo A, Kampmann C, Linhart A, Sunder-Plassman G, Houge G, Ramaswani U, Gal A & Mehta A. Fabry disease: overall effects of agalsidase alfa treatment. *European Journal of Clinical Investigation* 2004, 34, 838-844
- Cable W J, Kolodny E H, Adams R D. Fabry disease, impaired autonomic function. *Neurology* 1982; 32: 498-502
- Deegan PB, Baehner AF, Barba Romero MA, Hughes DA, Kampmann C, Beck M; European FOS Investigators. Natural history of Fabry disease in females in the Fabry Outcome Survey. *J Med Genet.* 2006 Apr;43(4):347-52.
- Dehout, F., Roland, D., Treille de Granseigne., Guillaume, B., and Van Maldergem., L Relief of gastrointestinal symptoms under enzyme replacement therapy (corrected) in patients with Fabry disease *J Inherit Metab Dis.* 2004;27(4):499-505. Erratum in: *J Inherit Metab Dis.* 2004;27(5):620.
- Desnick RJ, Ioannou YA, Eng CM: α -Galactosidase A deficiency: Fabry disease. In: *The Metabolic and Molecular Basis of Inherited disease.* 8th Edition, Vol. 3. Scriver CR, Beaudet AI, Sly WS, Valk D. (Eds) McGraw Hill, New York, (2001): 3733-3774.
- Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *American Journal of Cardiology.* 1986;57(6):450-458.
- Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation.* 1977;55(4):613-618.
- Eng C M, Guffon N, Wilcox W R, et al. Safety and efficacy of recombinant human α -galactosidase A replacement in Fabry disease. *N Engl J Med* 2001; 345: 9-16
- Garman, S.C, and Garbocz.i D.N. The molecular defect leading to Fabry disease:

structure of human alpha-galactosidase. *J Mol Biol* 2004; 337: 319-335

Germain DP, Waldek S, Banikazemi M, Bushinsky DA, Charrow J, Desnick RJ, Lee P, Loew T, Vedder AC, Abichandani R, Wilcox WR, Guffon N. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. *J Am Soc Nephrol*. 2007 May;18(5):1547-57.

Grabowski GA, Leslie N, Wenstrup R. Enzyme therapy for Gaucher's disease: the first 5 years. *Blood Reviews*, (1998), 12, 115-133.

Grewal R P, Barton N W. Fabry's disease presenting with stroke. *Clin Neuro Neurosurg* 1992; 94 (2): 77-9

Hajioff D, Enever Y, Quiney Y, Zuckerman J, MacDermott K & Mehta A. Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. *Journal of Inherited and Metabolic Diseases*, 2003., 26, 8, 787-794.

Hiltz, M.J., Brys, M., Marthol, H., Stemper, B., Dutsch, M., Enzyme replacement therapy improves the function of C-, A δ and A β nerve fibre in Fabry Neuropathy. *Neurology*, 62, 1066-1072, 2004

Lee J-K, Kim G-H, Kim J-S, et al. Identification of four novel mutations in five unrelated Korean families with Fabry disease. *Clin Genet* 2000; 58 (3): 228-33

Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M & Beck M. On behalf of the FOS investigators. Fabry disease defined: baseline clinical manifestations of 366 patients in FOS – the Fabry Outcome Survey. *European Journal of Clinical Investigation*, 2004, 34, 236-42.

Linthorst G E, Hollak C E M, Donker-Koopman W E, Strijland A , Aerts J M F G. Enzyme therapy for Fabry disease: Neutralizing antibodies toward agalsidase alpha and beta. *Kidney International*, 2004, 66, 1589-1595.

Mehta A, Lewis S and Lavery C. Treatment of lysosomal storage disorders. (Editorial) *British Medical Journal*, 2003, 327, 462-463.

MacDermot K D, Holmes A, Miners A H. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet* 2001(a); 38: 750-60

(MacDermot K D, Holmes A, Miners A H. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001(b); 38: 769-75

Meikle P J, Hopwood J J, Clague A E, Carey W F. Prevalence of lysosomal storage disorders. *JAMA* 1999; 281: 249-54

Mitsias P, Levine S R. Cerebrovascular complications of Fabry's disease. *Ann Neurol* 1996; 40 (1): 8-17

(Moore D F, Herscovitch P, Schiffmann R. Selective arterial distribution of cerebral hyperperfusion in Fabry disease. *J Neuroimaging* 2001(a); 11 (3): 303-7

(Moore D F, Scott L T, Gladwin M T, et al. Regional cerebral hyperperfusion and nitric oxide pathway deregulation in Fabry disease: reversal by enzyme replacement therapy. *Circulation* 2001(b); 104: 1506-12

Moore D F, Altarescu A, Ling G S F, et al. Cerebrovascular hyperdynamicity in Fabry disease with reversal following enzyme replacement therapy. *Stroke* 2002; 33 (2): 525-31

Morgan SH, Crawford MA. Anderson-Fabry disease. *Brit Med J.* 1988, 297, 872-873.

Nakao S, Takenaka T, Maeda M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med* 1995; 333: 288-93

Ohshima T, Murray GJ, Swaim WD et al. Alpha-galactosidase A deficient mice: a model of Fabry disease. *Proc. Natl. Acad. Sci. USA.* (1997) 94 (6), 2540 – 2544.

Pastores G M, Thadhani R. Enzyme replacement therapy for Anderson-Fabry disease. *Lancet* 2001; 358: 601-603

Pastores G M, Thadhani R. Advances in the management of Anderson-Fabry disease: enzyme replacement therapy. *Expert Opin Biol Ther* 2002; 2 (3): 1-9

Peters F P J, Vermeulen A, Kho T L. Anderson-Fabry's disease: α -galactosidase deficiency. *Lancet* 2001; 357: 138-40

Poorthuis B J, Wevers R A, Kleijer W J, et al. The frequency of lysosomal storage diseases in the Netherlands. *Hum Genet* 1999; 105: 151-6

Ramaswami U, S Wendt, G Pintos-Morell, R Parini, C Whybra, JA Leon Leal, F Santus and M Beck. Enzyme Replacement Therapy with Agalsidase Alfa in children with Fabry Disease. *Acta Paediatrica* 2007; 96: 122-7

Ries, M., Ramaswami, U et al. The early clinical phenotype of Fabry disease: A study of 35 European children. *Eur J Pediatr* 2003; 162: 767-772.

Rosenberg D M, Ferrans V J, Fulmer J D, et al. Chronic airflow obstruction in Fabry's disease. *Am J Med* 1980; 68: 898-905

Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation* 2002; 105; 1407-11

Schaeffer E, Gal A & Mehta A. Genotype phenotype correlations in Fabry Disease *Acta Paediatrica*, 2004.

Schiffman R, Kopp J B, Austin A H 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomised controlled trial. *JAMA* 2001; 285: 2743-9

Shelley E D, Shelley W B, Kurczynski T W. Painful fingers, heat intolerance, telangiectases of the ear: easily ignored childhood signs of Fabry disease. *Pediatr Dermatol* 1995; 12: 215-19

Sher N A, Letson R D, Desnick R J. The ocular manifestations of Fabry's disease. *Arch Ophthalmol* 1979; 97: 671-6

Spinelli L, Pisani A, Sabbatini M, Petretta M, Andreucci MV, Procaccini D, Lo Surdo N, Federico S, Cianciaruso B. Enzyme replacement therapy with agalsidase b improves cardiac involvement in Fabry's disease. *Clin Genet* 2004 1-8

Tsakiris D, Simpson H K L, Jones E H P, et al. Rare diseases in renal replacement therapy in the ERA-EDTA Registry. *Nephrol Dial Transplant* 1996; 11: 4-20

Waldek, S., PR interval and the response to enzyme replacement therapy for Fabry's disease. *New England Journal of Medicine* 348: 1186-1187 2003

Frank Weidemann, MD*; Frank Breunig, MD*; Meinrad Beer, MD; Joern Sandstede, MD; Oliver Turschner, MD; Wolfram Voelker, MD; Georg Ertl, MD; Anita Knoll, MD; Christoph Wanner, MD; Jörg M. Strotmann, MD Improvement of Cardiac Function During Enzyme Replacement Therapy in Patients With Fabry Disease A Prospective Strain Rate Imaging Study *Circulation*. 2003;108:1299-1301.)

Whybra C, Wendrich K, Ries M, Gal A, Beck M. Clinical manifestations in female Fabry disease patients, Schieppati A, Daina E, Sessa A, Remuzzi G (Eds.). *Rare kidney diseases. Contrib Nephrol. Basel, Karger, 2001, 136, 245 – 250.*

Whybra C, Kampmann C, Krummenauer F, Ries M, Mengel E, Miebach E, Baehner F, Kim K, Bajbouj M, Schwarting A, Gal A, Beck M 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 1-9

Wraith JE, Tytki-Szymanska A, Guffon N, Lien YH, Tsimaratos M, Vellodi A, Germain DP. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. *J Pediatr*. 2008 Apr;152(4):563-70, 570.e1.

APPENDIX 1

Fabry Disease: Paediatric Patients

Baseline Assessment at Diagnosis, Presentation or commencement of therapy:

General

1. Medical history and family pedigree
2. Clinical examination including growth chart
3. Vital signs
4. Pain score (BPI) – paediatric specific BPI/Varney-Thompson Paediatric Pain Questionnaire
5. Age appropriate Quality of Life scores (KINDL questionnaires/SF36/EQ5D)

Cardiac:

1. ECG
2. 24 hour ECG whenever possible (we monitor heart rate variability to assess autonomic function)
3. Echocardiogram

Renal:

1. Glomerular Filtration Rate: Cr51 EDTA –
Once every two years and calculate eGFR by Counahan- Barratt method on alternative years.
2. Twenty Four Hour urine protein – when potty trained and co-operative.
(Optional).
3. Spot urine Alb:Cr ratio; protein: creatinine ratio
4. Urine CTH (10 mls of urine in a universal container sent either immediately or frozen as for blood).
- 5.. Renal biopsy- if clinically indicated only (for example: persistent unexplained haematuria and/or persistent nephrotic range proteinuria).

Neurology

1. MRI brain examination (children not requiring sedation or if clinically indicated)

Ophthalmology:

1. Slit-lamp examination (cornea verticillata)
2. Retroillumination (AFD cataract)
3. Retinal examination (vascular abnormalities)
4. Retinal photography whenever possible.

Audiology:

< 5 years

Age appropriate test as suggested by audiology department (eg: Visual reinforced audiometry, Oto-acoustic emissions, distraction testing or Auditory Brain Stem response as applicable)

> 5 years:

Pure tone audiogram

Laboratory Investigations (blood):

1. Full blood count
2. Urea & electrolytes
3. Liver function tests
5. Plasma CTH (5 mls of blood in a lithium-heparin tube separated and sent immediately or frozen and transported frozen).
6. baseline sample for antibodies prior to starting ERT.

Criteria for ERT for children under 18 years of age

Pain is often a first manifestation of the disease and therapy started at this stage is also intended to arrest progression to involvement of other organ systems.

There are currently no published data on the efficacy of ERT in children, although there have been clear indications of improvement in both pain scores and quality of life, on ERT with Replagal or Fabrazyme (personal experiences of the

paediatricians in the LSD group). Recent publications have shown that ERT is safe even in young children. The emphasis of the inclusion criteria for ERT in adults and children is different, as it is very rare for children to develop cardiomyopathy, significant proteinuria or arrhythmias. However, pain and QoL are important, and would be considered as more important and relevant indications for treatment. Fabry Disease, particularly in males, is a progressive disease, and end organ failure is inevitable in early to mid adulthood.

Children with Fabry Disease, should be considered for treatment if :

1. Uncontrolled pain leading to a need to alter lifestyle or pain that interferes with quality of life.
2. Severe asthenia interfering with normal activities, including school attendance.
3. Gastroenterological symptoms such as pain, vomiting or altered bowel habit
4. Abnormal cerebral MRI scans with no clinical symptoms of CNS disease
6. Intra-ventricular conduction defects
7. Poor growth that cannot be accounted for.

Children fulfilling any of the criteria suggested for treatment in adults (defined above), would reflect a severe disease, and in these circumstances immediate treatment is recommended.

Exclusion Criteria for Enzyme Replacement Therapy in children \leq 18 years:

1. The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy.
2. Pregnant or lactating
3. Patient deemed too sick

Delivery of Enzyme Replacement Therapy:

Patients will be offered either Replagal or Fabrazyme.

1. Replagal 0.2 mg/kg in 100 mls of saline over 40 minutes, or
2. Fabrazyme 1.0 mg/kg in 500 mls of saline over 4 hours, reducing to 90 minutes as tolerated.

Only complete vials should be used, as no drug should be wasted. ERT with Replagal, the actual dose should be calculated if weight below 30kg. However, to avoid wastage of vials, differential doses can be given. For example, if a child required 3 vials of ERT, one could administer 1 vial alternating with 2 vials fortnightly, ensuring a total monthly dose of 3 vials. This dosing schedule has been used successfully in paediatric patients with Fabry Disease with no adverse outcome or worsening of their clinical symptoms (Ramaswami personal observation).

Pre-medication with paracetamol, chlorpheniramine, hydroxyzine or hydrocortisone will be given at the discretion of the prescribing clinician.

The first (1-3) 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 pre-medication as above.

When the clinician is confident that infusions will proceed without serious or life-threatening reaction then patients may be offered home infusion therapy.

This will be initiated by an accredited home care nursing service but ultimately, after appropriate training, enzyme may be administered by the patient's parents or carers, if appropriate. Persistent reaction to enzyme infusion should be assessed by the clinician and the existence of antibodies to alpha-galactosidase A investigated. In the case of anaphylactic-type reactions this should be treated as a medical emergency, infusions suspended and the existence of IgE antibodies immediately investigated.

Paediatric Follow up

For patients receiving enzyme replacement therapy:

If patient are receiving shared care with a local centre, then the responsibility for result interpretation, treatment decisions and dose adjustment will rest with the NSCAG-designated centre. Protocols for management of shared care patients should be available. If patients are on home therapy, follow up and regular updates from home care delivery services must be reviewed and appropriate action plans must be taken by the designated NSCAG centre.

Patients on ERT will be reviewed every 6 months in out-patients.

Six monthly visit:

Clinical examination and vital signs

Plasma and urinary CTH

Antibody assays

Pain score (BPI) – paediatric specific BPI or the Varney-Thompson Paediatric Pain Questionnaire.

Age appropriate Quality of Life scores (KINDL questionnaires/ SF36/EQ5D)

Other baseline investigations may need to be repeated if clinically indicated

12 months visit (and annually thereafter):

All baseline investigations, unless investigations are indicated earlier.

Efficacy End Points

An improvement in or a prevention of deterioration:

8. Age appropriate pain scores

9. Age appropriate Quality of Life measurement including school attendance.

10. Growth and development

11. Cardiac structure and function (if abnormal at baseline)

12. Renal Function if abnormal at baseline(significant Proteinuria, reduced GFR at baseline)

Nb: Normal cardiac and renal function during annual reviews of children on ERT may reflect a prevention of disease progression.

Exit Criteria

a. Treatment will be discontinued if the patient develops a life-threatening complication unlikely to benefit from further ERT. For example, severe infusion associated reactions not controlled by other means.

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

c) Evidence of disease progression despite regular therapy