Therapeutic goals in the treatment of Fabry disease

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Purpose: Fabry disease is a progressive multiorgan, multisystem disorder that is caused by a deficiency in the lysosomal enzyme α-galactosidase A. Serious renal, cardiac, and cerebrovascular involvement are responsible for much of the morbidity and premature mortality associated with Fabry disease, and neuropathic pain, gastrointestinal problems, and hypohidrosis negatively affect quality of life of patients with Fabry disease. Fabry disease is X-linked, but women are often symptomatic and may be as severely affected as men. **Methods:** We propose a series of therapeutic and symptomatic goals for use in setting the expectations of enzyme replacement therapy and for assessing the response to enzyme replacement therapy in the treatment of Fabry disease. **Results:** Enzyme replacement therapy has been available since 2001 and has been associated with benefit in clinical trials, including stabilization of kidney function, improvement of cardiac structure and function, reduction in severity of neuropathic pain, and improvement in gastrointestinal involvement. **Conclusions:** The presentation of these therapeutic goals will aid in the evaluation of response to enzyme replacement therapy and be useful in establishing an overall management plan for individual patients. ***Genet Med*** **2010:12(11):713–720.**

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Fabry disease is an X-linked metabolic disorder caused by a deficiency in the lysosomal enzyme, α-galactosidase A (αGalA).[1] In patients with Fabry disease, the enzyme substrate globotriaosylceramide (Gb3) accumulates in cells and participates in the progressive multiorgan pathology of the disease.[2] The incidence of Fabry disease is approximately 1 in 117,000 live births,[3] but recent newborn screening efforts suggest that the incidence of mutations in the *αGalA* gene may be much higher, approximately 1 in 3,100.[4]

The signs and symptoms of Fabry disease emerge in childhood and adolescence and typically include episodes of neuropathic pain, gastrointestinal disturbances, angiokeratomas, and hypohidrosis.[5–7] Kidney dysfunction, cardiac valve disease, cardiomyopathy, and stroke increase in prevalence in adults,[2] resulting in a substantial reduction in health-related quality of life[8–10] and an increase in premature mortality.[11,12] Despite being X-linked, heterozygous women may experience all the signs and symptoms of Fabry disease that are seen in men[12–15]; although compared with hemizygous males, signs and symptoms of Fabry disease in women typically emerge at an older age and with less severity.

ENZYME REPLACEMENT THERAPY

Treatment of Fabry disease with αGalA has been commercially available since 2001. Two formulations of αGalA are available, agalsidase alfa (Replagal®, Shire Human Genetic Therapies, Inc., Cambridge, MA) and agalsidase beta (Fabrazyme®, Genzyme Corporation, Cambridge, MA). Agalsidase alfa is produced in a human cell line by gene activation[16,17] and is dosed at 0.2 mg/kg every other week. Agalsidase beta is produced in Chinese hamster ovary cells and is dosed at 1.0 mg/kg every other week with premedication consisting of an antipyretic and/or antihistamine.

The clinical experience with enzyme replacement therapy (ERT) for Fabry disease has continued to grow since its introduction. In 2006, Eng et al.[18] published the initial guidelines for the evaluation and management of Fabry disease. In the accompanying report,[19] we have reviewed the key clinical studies of ERT in Fabry disease and summarized the evidence of benefit for both agalsidase alfa and agalsidase beta. In this report, we have extended the work of Eng et al.[18] on the basis of the additional clinical data that have been published and propose a series of therapeutic goals based on this evidence to aid the clinician in setting expectations and evaluating the response to ERT in Fabry disease.

MATERIALS AND METHODS

In April 2009, Shire Human Genetic Therapies, Inc. (Shire HGT, Cambridge, MA) invited an international group of physicians with extensive clinical experience in the management and treatment of Fabry disease to a meeting in Frankfurt, Germany, to discuss evidence relating to the use of ERT in treatment of Fabry disease and to propose treatment goals. These experts practice in different parts of Europe, North America, Australia, and South America and have a spectrum of relevant specialty expertise, including cardiology, nephrology, neurology, pediatrics, genetics, metabolism, and hematology. A draft review was prepared by an independent coordinator and then discussed and amended during the course of a second meeting in Barcelona, Spain, in November 2009. This review represents the consensus position of those discussions.

RESULTS

Therapeutic goals

The signs and symptoms of Fabry disease affect many organs and systems and are generally progressive in nature. When evalu-

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ating the responses to ERT, it is important to recognize that a therapeutic response may involve stabilization or slowing of the progression of certain pathologies, with the goal of preservation of organ function rather than reversing dysfunction. The treatment goals presented in this review are based on the evidence presented in the accompanying report[19] and on the extensive clinical experience of the members of the panel. The order of presentation reflects the impact of the organ or system on the morbidity and premature mortality associated with Fabry disease. Thus, kidney, heart, and cerebrovascular involvement are discussed first, followed by pain, sweat function, quality of life, and gastrointestinal symptoms. In some cases, treatment goals are presented without evidence for an effect of ERT. Such is the case when adjunct therapy may be able to influence the disease course (e.g., use of antiplatelet medication for reducing the risk of stroke).

Biomarkers

Plasma and urine levels of Gb3 are elevated in patients with Fabry disease. The elevations are smaller in women than in men, and levels are often within the normal range.[20] Plasma and urine levels of Gb3 decrease during ERT in men, women, and children with Fabry disease (e.g., Refs. 20–24). Despite this response, plasma and urine Gb3 cannot be considered suitable biomarkers of clinical efficacy because baseline levels do not correlate with disease severity, and changes during ERT are not predictive of clinical efficacy.[25] At the best, changes in these levels serve as an indicator (i.e., proof of principle) that infused enzyme is active. In adult and pediatric males, a maximum reduction in plasma Gb3 of approximately 50% has been reported with either agalsidase alfa[21,23] or agalsidase beta,[22] and such a decrease should be considered as useful when monitoring the response to ERT. Although reductions in plasma and urine Gb3 in women have been reported with ERT,[20] substantial overlap with the normal range reduces their utility in monitoring enzyme activity during ERT.

Kidney disease

Progressive kidney dysfunction is responsible for much of the morbidity and premature mortality of Fabry disease, especially in men, in whom it is nearly universal. The initial sign of kidney disease in patients with Fabry disease is proteinuria or microalbuminuria, which is seen in more than half of men by the age of 35 years[26] and has been reported in children.[5] Hyperfiltration (i.e., glomerular filtration rate (GFR) >135 mL/minute/1.73 m^2) may also be an initial sign of kidney dysfunction.[27,28] Once kidney dysfunction begins in men, GFR is progressively lost, and progression to end-stage renal disease (ESRD) is inevitable without treatment. The rate of loss of GFR in untreated men with Fabry disease has been estimated to be between 3.0 mL/minute/1.73 m^2/year[29] and 12.2 mL/minute/year.[26] A single study has reported serial measurement (as opposed to estimates) of GFR in placebo-treated patients enrolled in clinical trials. In 54 patients who had GFR measured before and after a 6-month placebo period, a rate of decline in GFR of 7.0 $\pm$ 32.9 mL/minute/1.73 m^2/year was observed.[26] The rate of loss of GFR in women with Fabry disease is less than that seen in men,[29] and fewer women progress to ESRD.[15,30,31] In both men and women, the presence of proteinuria $\geq$1 g/24 hours is a risk factor for more rapid progression of loss of GFR.[30]

Several clinical studies support the concept that ERT stabilizes kidney function in Fabry disease and that this protective effect is more prominent in patients with less advanced kidney dysfunction. West et al.[28] performed a summary analysis of the effects of agalsidase alfa on kidney function in male patients who had participated in three separate double-blinded clinical trials and their open-labeled extension studies. Eighty-five patients were treated with agalsidase alfa for at least 1 year (mean: 2.1 years) and demonstrated a rate of loss of GFR of 2.9 $\pm$ 8.7 mL/minute/1.73 m^2/year (mean $\pm$ SD) during their treatment period, a value that was less than that observed during the placebo period (see earlier). Proteinuria $\geq$1 g/day was a significant risk factor for continued rapid decline of GFR during treatment. Similarly, Germain et al.[31] reported that agalsidase beta stabilized estimated GFR (eGFR) in 58 patients treated for up to 4.5 years and that proteinuria $>$1 g/day was also a risk factor for failure to respond. Neither agalsidase alfa nor agalsidase beta seems to influence proteinuria in men, although in female patients, agalsidase alfa significantly reduced proteinuria in 11 women with baseline proteinuria $>$300 mg/day after 3 years.[20] Agalsidase beta was associated with a nonsignificant reduction in the hazard ratio of experiencing a major clinical event in patients with mild-to-moderate baseline kidney dysfunction.[33] No effect of agalsidase beta on eGFR was seen during this study.

Kidney therapeutic goals

Because kidney disease is responsible for much of the morbidity and premature mortality of Fabry disease, all patients with Fabry disease with evidence of kidney disease should be aggressively treated. Proteinuria is often the initial sign of kidney disease and should be considered sufficient evidence of kidney involvement to initiate ERT. Although the major studies have shown that proteinuria in excess of 1 g/day is a significant risk factor for continued loss of GFR during ERT, a lower threshold can be supported by the data. For example, in the recent report by Schiffmann et al.,[29] a negative influence of proteinuria at levels between 0.1 and 1 g/day in untreated male and female patients was observed. Similarly, the analyses of West et al.[27] showed a smaller response to ERT in patients with baseline proteinuria between 0.3 and 1 g/day compared with the response of patients with baseline proteinuria $<$0.3 g/day. Thus, ERT should be initiated in all patients with proteinuria $>$0.3 g/day or who have demonstrated a reduction in GFR to $<$90 mL/minute/1.73 m^2 in the absence of proteinuria. Hyperfiltration may be the initial sign of kidney disease,[27,28] and patients with GFR $>$135 mL/minute/1.73 m^2 should be considered for ERT. In patients with proteinuria, the addition of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker may reduce the protein excretion level and increase the renal response to ERT.[34] However, it is important to realize that most patients with Fabry disease have normal blood pressure and may not tolerate the doses of these agents needed to control proteinuria.

Treatment goals are dependent on the initial renal function of each patient (Table 1). Patients should be monitored every 6 months. Although measured GFR is the preferred method of monitoring changes in GFR, eGFR[35] may be adequate in adults provided that the physician realizes that eGFR may overestimate measured GFR by as much as 26%.[27] Thus, a patient who has an eGFR within the normal range ($>$90 mL/minute/1.73 m^2) may in reality have a measured GFR indicative of mild kidney dysfunction (60–90 mL/minute/1.73 m^2).

The method of Schwartz et al.[36] of estimating GFR in children substantially overestimates actual GFR in children with Fabry disease,[37] especially is the vast majority of children whose renal function in not impaired. The new equation described by Schwartz et al.[38] or the older Counahan-Barratt equation[39] provides relatively good agreement with measured GFR in children with Fabry disease[37] and should be used for monitoring changes in eGFR in children.

Although the goal of ERT is to stop the loss of GFR, it is difficult to attain this goal based on the fact that the adult population without Fabry disease loses approximately 1 mL/

Table 1 Treatment goals for kidney

Patient subgroup	Treatment goals
GFR >135 mL/min/1.73 m^2 (hyperfiltration)	Reduction of GFR into the normal range (90–135 mL/min/1.73 m^2)
GFR ≥90 and ≤135 mL/min/1.73 m^2	Maintain GFR within normal range
	A loss of GFR of ≤1 mL/min/1.73 m^2/yr
	Stability of GFR in pediatric patients
GFR <90 mL/min/1.73 m^2	A loss of GFR ≤2 mL/min/1.73 m^2/yr for men and ≤1 mL/min/1.73 m^2/yr in women
Patients with proteinuria >0.3 g/day	No increase in proteinuria
Patients with proteinuria ≥1 g/day	Reduction of proteinuria to <1 g/day with ACE inhibitors and/or angiotensin receptor blockers

GFR, glomerular filtration rate; ACE, angiotensin converting enzyme.

minute/1.73 m^2/year.[40] Thus, setting a goal to restrict GFR loss to no more than 2 mL/minute/1.73 m^2/year in men and to no more than 1 mL/minute/1.73 m^2/year in women may be more reasonable. A goal of no more than 1 mL/minute/1.73 m^2/year is appropriate for men who do not have proteinuria or in whom proteinuria has been well controlled with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In children, the goal should be to maintain stability of eGFR. Ultimately, a delay in time to renal failure or need for dialysis or transplantation may be achieved.

Cardiac disease

Cardiac involvement is common in patients with Fabry disease and includes left ventricular hypertrophy (LVH), valvular dysfunction, and arrhythmias.[41–44] Cardiomyopathy typically has its clinical onset in men between the ages of 20 and 30 years and approximately 10 years later in women.[42] LVH is common; in the Fabry Outcome Survey (FOS), LVH was found in 33% of untreated women and 53% of untreated men.[44] In a study of 39 male and 39 female untreated patients with Fabry disease who were not receiving ERT and who had at least two echocardiographic examinations between 1 and 9 years apart, the average rate of progression of left ventricular mass (LVM) indexed to height in men and women was 4.07 ± 1.03 g/$m^{2.7}$/year and 2.31 ± 0.81 g/$m^{2.7}$/year, respectively.[42] Progressive valvular involvement is common. In a longitudinal study of 60 patients with Fabry disease, the prevalence of mild mitral insufficiency increased from 34 (56.7%) at baseline to 49 (81.6%) after a mean 2.7-year follow-up period.[45] Similar progression was noted for mild tricuspid involvement. In FOS, 32.6% of men and 38.3% of women who were receiving ERT had a history of palpitations or documented arrhythmia with an average age of onset of 37.2 years in men and 43.8 years in women.[44] Although ejection fraction is typically normal,[42] heart failure is reported in 19–25% of men with Fabry disease and in 20–30% of women.[44] In the later stages of progression, fibrosis may be prominent.[46,47] Fibrosis is considered to be irreversible. Cardiac involvement is a common cause of death in both men and women with Fabry disease.[48,49]

The effect of agalsidase alfa on cardiac morphometry has been reported in four studies. In a 6-month double-blinded, placebo-controlled clinical trial in 15 men with Fabry disease, Hughes et al.[50] reported a significant reduction in LVM measured by magnetic resonance imaging compared with placebo. Kampmann et al.[51] reported that agalsidase alfa reduced LVM in patients with baseline LVH during 1–3 years of treatment. In women with baseline LVH, Whybra et al.[20] found a persistent reduction in LVM during a 4-year study. A recent report from FOS showed that 5 years of agalsidase alfa resulted in sustained and significant reductions in LVM.[52] Agalsidase beta has been studied in 10 open-labeled, noncontrolled trials with mixed results. Three studies found no effect,[53–55] whereas the other seven reported varying degrees of reduction in LVM.[46,47,56–60] Importantly, the results of these studies suggest that early initiation of therapy leads to a better response. For example, Beer et al.[47] found a reduction in LVM only in patients without myocardial fibrosis at baseline. Weidemann et al.[46] reported that 3 years of agalsidase beta reduced LVM but that functional improvement was seen only in patients without fibrosis.

In addition to ERT, other concomitant therapy is indicated in the management of cardiac involvement of Fabry disease. For example, symptomatic bradycardia due to significant atrioventricular block may require pacemaker implantation, and an implantable cardioverter defibrillator is indicated in the management of malignant ventricular arrhythmias.[61]

Treatment goals

Patients with evidence of cardiac involvement should be considered candidates for ERT. The goals of ERT in patients with cardiac involvement are the reduction of LVM in patients with LVH, the improvement of left ventricular functional parameters in patients with compromised function, and the improvement of arrhythmias in patients with baseline rhythm disturbances (Table 2). Although reduction of LVM may occur in patients with myocardial fibrosis, improvement in functional

Table 2 Treatment goals for heart

Patient subgroup	Treatment goals
Patients with cardiomyopathy (LVMi >51 g/$m^{2.7}$ in men and >48 g/$m^{2.7}$ in women)	Reduction of LVM into the normal range
Patients without cardiac involvement	Preservation of normal structure and function
Patients with heart failure	Improvement of functional class using standard assessment instruments
Patients with rhythm disturbances	Reduction in frequency and severity

LVMi, left ventricular mass indexed to height (g/$m^{2.7}$); LVM, left ventricular mass.

parameters is not expected.[46] In patients without cardiac involvement, the goals of ERT should be the preservation of normal structure and function. It is suggested that left ventricular structure and function be assessed at least yearly by echocardiography. Tissue Doppler imaging may be useful in identifying patients at risk for progressive cardiomyopathy.[62] Standard assessments of heart failure (e.g., New York Heart Association classification of heart failure) should be conducted at the same time as the echocardiographic examination with the goal of improving or stabilizing function. Ultimately, the goals would be to reduce cardiac-related morbidity or death, and/or delay time to pacemaker/defibrillator placement.

Cerebrovascular involvement

Stroke is common in patients with Fabry disease.[29,63] In FOS, 9% of men and 5% of women have a history of stroke with a mean age of onset of 39.2 years in men and 51.4 years in women.[48] In the Fabry Registry, 6.9% of men and 4.3% of women experienced stroke before initiation of ERT, with an average age at first stroke of 39.8 years in men and 45.7 years in women.[63] Similarly, a high frequency of Fabry disease (4.9% of men and 2.4% of women) was found in a population of patients who had experienced a cryptogenic cerebrovascular event.[64] These estimates may be high because of the inclusion of patients with multiple ischemic events. Two other studies suggest that Fabry disease is responsible for a lower fraction of cryptogenic stroke (0%[65] and 0.65%[66]). Stroke is often the first manifestation of major organ involvement in patients with Fabry disease, and 46% of patients experienced stroke before being diagnosed with Fabry disease.[63] Ischemic strokes are reported to account for 86.8% of first stroke in patients with Fabry disease, a percentage that is similar to that seen in the general population.[63]

Elevated blood pressure is a risk factor for stroke and transient ischemic attack (TIA) in the non-Fabry population, and it should be assumed that hypertension contributes to their incidence in patients with Fabry disease. In FOS, agalsidase alfa has been reported to significantly reduce both systolic and diastolic blood pressure and to reduce the prevalence of hypertension,[52,67] but it is not known whether these effects will translate to a reduced incidence of cerebrovascular events. Strokes have been reported in some patients in nearly all clinical trials of ERT.[20,21,32] Changes in cerebral blood flow have been reported in patients treated with agalsidase alfa,[68–70] but the clinical relevance of these responses is not known.

Cerebrovascular treatment goals

All patients with Fabry disease who have a history of stroke or TIA should receive ERT. In addition, all patients should be considered as having a high risk of stroke, and adjunct therapies are appropriate. Antiplatelet drugs should be used because of the high risk of ischemic stroke. Statins may be protective in patients with Fabry disease who have had a stroke, who have white matter lesions but with normal neurologic function, or who have high levels of prothrombotic markers.[71] Antihypertensive agents should be used to achieve recommended blood pressure targets in all patients with hypertension. No evidence of benefit of ERT on the incidence of stroke or TIA has been reported, but the goal of ERT should be the prevention or delay of these events (Table 3).

Table 3 Treatment goals for cerebrovascular events

Patient subgroup	Treatment goals
All patients with Fabry disease	Reduction of the incidence of stroke and transient ischemic attacks

Pain and quality of life

Neurologic pain is a frequent symptom in both male and female patients with Fabry disease and may be the initial symptom experienced by a patient with Fabry disease. In FOS, neurologic pain was reported by 81.4% of men and 65.3% of women, with a mean age of onset of 14.8 years in men and 19.8 years in women.[72] In the Fabry Registry, neurologic pain was reported by 62% of men and 41% of women, with a median age of onset of 9 years in men and 10 years in women.[43] In studies of pediatric patients, neuropathic pain or acroparesthesia was reported in 63% of boys and 46% of girls[5–7,73,74] (reviewed by Pintos-Morell and Beck[75]). The pain most often occurs in the hands and feet and has been described as agonizing, burning, tingling, and lancinating.[76] Neuropathic pain due to Fabry disease is often managed with anticonvulsant drugs (e.g., carbamazepine or phenytoin),[77] because conventional analgesics and narcotic analgesics are relatively ineffective.

The impact of Fabry disease on health-related quality of life is substantial. Gold et al.[8] reported that scores in all domains of the Short Form-36 Health Survey for men with Fabry disease were worse than those found in the general US population. Similar findings were reported for male patients with Fabry disease compared with the general male population of the United Kingdom.[9] Women with Fabry disease also experience reduced health-related quality of life.[10,15,78] When compared with patients with other chronic diseases, the reduction in quality of life for men with Fabry disease is roughly the same as reported for men with human immunodeficiency virus-acquired immunodeficiency syndrome and is worse than seen in men with ESRD or stroke.[8] In women, quality of life is comparable with that observed in women with rheumatoid arthritis or multiple sclerosis.[10,78]

Agalsidase alfa was reported to reduce the severity of neuropathic pain in men in a double-blinded, placebo-controlled study[79] and in women was reported to reduce neuropathic pain intensity after 12 months of treatment, a response that was sustained through 4 years.[20] Improvement in pain scores has also been observed for patients treated with agalsidase alfa enrolled in FOS.[80] In children, agalsidase alfa reduced the need for pain medication[22] and reduced pain scores.[24,73] In women with Fabry disease, agalsidase alfa improved the Short Form-36 physical summary score and role-physical and general health scores.[78] A study of 13 men with Fabry disease treated with agalsidase beta found improvements in the mental component and general health scores of the Short Form-36.[81] Agalsidase beta was reported to reduce the severity neuropathic pain compared with baseline values, but in this study, baseline pain scores were low, and the response was not different than the response observed in the placebo group.[82]

Treatment goals

Patients with neuropathic pain should be considered for ERT. Because of the major impact that pain has on patient's lives and quality of life, the goals of treatment should be to reduce and maintain pain at levels that have minimal impact on activities of daily living and to reduce the need for pain medications (Table 4). Patients should be evaluated periodically using a validated instrument for assessing pain (e.g., Brief Pain Inventory[83]). Patients on ERT will frequently require the use of anticonvulsant medications to control pain and, therefore, should be asked

Table 4 Treatment goals for pain

Patient subgroup	Treatment goals
Patients with severe neuropathic pain	Reduction of need for pain medication
	Reduction of pain level to level below where it interferes with activities of daily living (e.g., BPI "pain at its worst" score <5)[83]
Patients with minimal neuropathic pain	Maintenance or improvement of pain
Patients without neuropathic pain	Maintenance of pain status

BPI, Brief Pain Inventory.

to monitor their need for pain medications, preferably by keeping a pain and medication diary. Pain management is particularly important in children who often experience moderate or severe pain without receiving any treatment.[74]

Sweat function

Patients with Fabry disease commonly experience reduced sweat function that may reduce the capacity for physical activity and precipitate pain.[11,12] Objective measurement of sweat function using Quantitative Sudomotor Axon Reflex Test (QSART) has been used to demonstrate an acute (24–48 hours) improvement in sweating after agalsidase alfa in some patients.[84] In children, QSART was used to demonstrate an improvement in sweat volume for 0.48 ± 0.36 μL/mm^2 at baseline to 0.73 ± 0.68 μL/mm^2 after 6 months.[23]

Hyperhidrosis has also been documented in patients with Fabry disease. In FOS, the reported prevalence of hyperhidrosis is 6.4% in men and 11.9% in women.[85] The effect of ERT with agalsidase alfa has been reported for three patients with no effect in two patients and improvement in the few days after each infusion in the other patients.[85]

Treatment goals

The objective measurement of sweat function requires specialized equipment that will not be readily accessible for the majority of physicians. In addition, the reproducibility of QSART to measure small volumes may limit its utility to detect clinically important improvements in function.[86] The patient's subjective improvement may be considered a goal of treatment.

Gastrointestinal involvement

Gastrointestinal symptoms are commonly reported in patients with Fabry disease. In FOS, 52% of patients report experiencing gastrointestinal symptoms, including abdominal pain, diarrhea, constipation, nausea, and vomiting.[87] In the Fabry Registry, 19% of men and 13% of women reported gastroenterological problems, with a median age at onset of 8 and 14 years, respectively. Children seem to experience gastrointestinal problems more frequently than adults; for example, in the Fabry registry, 45% of boys and 18% of girls reported gastrointestinal problems.[74]

In one small study of agalsidase alfa, 7 of 10 patients reported reduction in the severity and frequency of abdominal pain after 6 months of agalsidase alfa, and five of six patients reported a reduction in the frequency of diarrhea.[88] A report from FOS documented reduction in the percentage of patients reporting abdominal pain or diarrhea after 1 or 2 years of agalsidase alfa.[87] Six to 7 months of agalsidase beta was reported to reduce gastrointestinal symptoms in four men with severe gastrointestinal involvement at baseline.[89] In children, 1 year of agalsidase beta significantly reduced the prevalence of postprandial pain and vomiting compared with baseline.[90] Weight gain has been reported with both agalsidase alfa and agalsidase beta.[59,79,90]

Table 5 Treatment goals for gastrointestinal involvement

Patient subgroup	Treatment goals
Patients with frequent diarrhea	Reduction in frequency of diarrhea
Patients with abdominal pain	Reduction in frequency and severity of abdominal pain

Gastrointestinal treatment goals

The goal of ERT should be to reduce the frequency and severity of gastrointestinal pain and diarrhea (Table 5). Because these symptoms may limit food intake and nutrition, positive response to ERT may be weight gain in some individuals.

Hearing

Hearing loss has been reported in 74% of patients with Fabry disease, and clinical hearing impairment has been reported in 16% of patients.[91] The increase in hearing thresholds has been found in all frequency ranges and increases with age.[91] The mechanism of hearing loss is primarily sensorineural, with conductive or mixed hearing loss contributing in approximately 25% of the cases.[91] Agalsidase alfa has been reported to improve hearing loss in patients with Fabry disease. Hajioff et al.[92] reported a significant improvement in high-frequency sensorineural hearing loss after 18 and 30 months of agalsidase alfa in a group of 15 adult male patients with Fabry disease. Similar findings were reported for patients in FOS who had baseline hearing loss and were treated with agalsidase alfa for a median of 12 months.[93]

Treatment goals

The goal of ERT should be to improve hearing in patients with baseline hearing loss and maintain hearing thresholds in patients at baseline within the normal range (Table 6).

Monitoring of overall disease burden

Two instruments have been described to monitor the overall symptom burden of Fabry disease: the Mainz Severity Score Index (MSSI)[94] and the Fabry disease severity scoring system (Fabry DS3).[95] The MSSI scores are assigned based on the prevalence of signs and symptoms in four general areas: general, neurologic, renal, and cardiovascular. The Fabry DS3 evaluates five domains, including peripheral nervous system, renal, cardiac, central nervous system, and patient reported overall well-being. With both instruments, a higher score represents a more severe overall disease burden.

Table 6 Treatment goals for hearing

Patient subgroup	Treatment goals
Patients with hearing loss	Improvement in hearing
Patients with normal hearing	Maintenance of normal hearing

Agalsidase alfa has been reported to be associated with a significant reduction in total MSSI score in women and men with Fabry disease.[20,94] No studies of the response to agalsidase beta have been reported for either the MSSI or Fabry DS3. These instruments may be appropriate for following the overall response to ERT, with the therapeutic goal being a reduction in total score. Stability of total score may also be considered a goal of ERT because of the progressive nature of untreated Fabry disease.

DISCUSSION

The initial clinical experience with ERT for Fabry disease is confounded by its pleomorphic features and the various stages of disease patients were in at the time of treatment initiation. The major challenges relate to evaluating the benefits of ERT beyond the clinical trial phase. For Gaucher disease, which is the most common lysosomal storage disease and the disorder with the longest experience with ERT, the development of therapeutic goals of treatment has aided the evaluation of clinical success of ERT in individual patients[96–98] and allowed the assessment of alternative treatments, such as substrate reduction therapy.[99] In addition, the extensive experience with ERT for Gaucher disease has also resulted in the development of treatment goals for specific patient populations, such as adults[96] and children.[98]

Compared with Gaucher disease, the evaluation of the response to ERT in Fabry disease is complicated by the fact that no obvious morphological changes occur in response to ERT and no ideal biomarkers that correlate with disease severity or clinical response to ERT have been identified. In Gaucher disease and Hunter syndrome, for example, the characteristic organomegaly is substantially reduced with ERT.[96,98,100] Similarly, the anemia and thrombocytopenia of Gaucher disease can be objectively monitored during ERT to assess the response to treatment. In Fabry disease, much of the critical organ pathology often remains subclinical until the late stages of the disease. Examples include kidney dysfunction and cardiomyopathy, and without regular and objective monitoring, it is difficult to establish that a clinical response to ERT has occurred in these critical organs.

The pathology of Fabry disease is progressive, and it is important to emphasize that a positive response to ERT may be represented by stability rather than improvement or reversal of the signs and symptoms of the disease. This concept has been clearly illustrated by the studies of the effect of ERT on kidney dysfunction in which stability of GFR (or eGFR) during ERT is considered a success, as this likely means a delay in the onset of renal failure or time to dialysis or transplant.[27,32]

Guidelines for the initiation of ERT in Fabry disease have been proposed by several groups (e.g., Refs. 18 and 101–104). These guidelines propose criteria for the initiation of ERT in patients with Fabry disease that are based primarily on the published evidence of efficacy. As expected, the country-specific guidelines vary according to the local health care system.[101–103] In general, these guidelines indicate that adult male patients should be treated starting at the time of diagnosis[18,101] or at the onset of symptoms or evidence of organ dysfunction.[102,103] Women with significant symptoms or evidence of organ dysfunction should also be treated.[18,101–103] Little evidence regarding when to initiate ERT in pediatric patients has been published, but these guidelines again suggest that children with "significant symptoms" should be considered for ERT.

The issue of treatment strategies in patients who fail to reach one or more therapeutic goals during ERT has not been established. In some patients with advanced disease, certain benefits of ERT may not be expected. For example, no benefit on renal function has been observed during ERT in patients with advanced kidney dysfunction as shown by proteinuria in excess of 1 g/day.[27,32] Similarly, little cardiac benefit has been reported in patients with myocardial fibrosis.[46,47] Despite the failure of these organ systems to respond to ERT, other benefits may still occur, and therefore, careful monitoring of these and other therapeutic goals should continue.

Children and women with Fabry disease have also been treated with ERT. Until more experience with ERT in women and children with Fabry disease is published, the therapeutic goals outlined in this report should be considered appropriate for these patient populations at this time. As more experience is gained in these distinct patient populations, it is likely that specific therapeutic goals will be developed.

CONCLUSIONS

Fabry disease is characterized by progressive multiorgan, multisystem pathology. The goal of ERT in Fabry disease is to slow or stop the progression of the disease, restore health-related quality of life, and prolong survival. The presentation of these therapeutic goals will aid in the evaluation of response to ERT and be useful in establishing an overall management plan for individual patients. It is anticipated that as the clinical experience with ERT increases, these therapeutic goals will be revised, and specific goals for ERT in women and pediatric patients will be developed.

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REFERENCES

1. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. *N Engl J Med* 1967;276:1163–1167.
2. Schiffmann R. Fabry disease. *Pharmacol Ther* 2009;122:65–77.
3. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999;281:249–254.
4. Spada M, Pagliardini S, Yasuda M, et al. High incidence of later-onset Fabry disease revealed by newborn screening. *Am J Hum Genet* 2006;79:31–40.
5. Ries M, Gupta S, Moore DF, et al. Pediatric Fabry disease. *Pediatrics* 2005;115:e344–e355.
6. Ries M, Ramaswami U, Parini R, et al. The early clinical phenotype of Fabry disease: a study on 35 European children and adolescents. *Eur J Pediatr* 2003;162:767–772.
7. Ramaswami U, Whybra C, Parini R, et al. Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey. *Acta Paediatr* 2006;95:86–92.
8. Gold KF, Pastores GM, Botteman MF, et al. Quality of life of patients with Fabry disease. *Qual Life Res* 2002;11:317–327.
9. Miners AH, Holmes A, Sherr L, Jenkinson C, MacDermot KD. Assessment of health-related quality-of-life in males with Anderson Fabry disease before therapeutic intervention. *Qual Life Res* 2002;11:127–133.
10. Street NJ, Yi MS, Bailey LA, Hopkin RJ. Comparison of health-related quality of life between heterozygous women with Fabry disease, a healthy control population, and patients with other chronic disease. *Genet Med* 2006;8:346–353.
11. 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;38:750–760.
12. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001;38:769–775.
13. Whybra C, Kampmann C, Willers I, et al. Anderson-Fabry disease: clinical manifestations of disease in female heterozygotes. *J Inherit Metab Dis* 2001;24:715–724.
14. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genet Med* 2007;9:34–45.
15. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. *Mol Genet Metab* 2008;93:112–128.
16. Schiffmann R, Murray GJ, Treco D, et al. Infusion of alpha-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. *Proc Natl Acad Sci USA* 2000;97:365–370.
17. Lee K, Jin X, Zhang K, et al. A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease. *Glycobiology* 2003;13:305–313.
18. Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet Med* 2006;8:539–548.
19. Lidove O, West ML, Pintos-Morell G, et al. Effects of enzyme replacement therapy in Fabry disease—a comprehensive review of the medical literature. *Genet Med* 2010;12:668–679.
20. Whybra C, Miebach E, Mengel E, et al. A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. *Genet Med* 2009;11:441–449.
21. Schiffmann R, Ries M, Timmons M, Flaherty JT, Brady RO. Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting. *Nephrol Dial Transplant* 2006;21:345–354.
22. Wilcox WR, Banikazemi M, Guffon N, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. *Am J Hum Genet* 2004;75:65–74.
23. Ries M, Clarke JT, Whybra C, et al. Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. *Pediatrics* 2006;118:924–932.
24. Schiffmann R, Martin RA, Reimschisel T, et al. Four-year prospective clinical trial of agalsidase alfa in children with Fabry disease. *J Pediatr* 2010;156:832–837, 837.e1.
25. Bekri S, Lidove O, Jaussaud R, Knebelmann B, Barbey F. The role of ceramide trihexoside (globotriaosylceramide) in the diagnosis and follow-up of the efficacy of treatment of Fabry disease: a review of the literature. *Cardiovasc Hematol Agents Med Chem* 2006;4:289–297.
26. Branton MH, Schiffmann R, Sabnis SG, et al. Natural history of Fabry renal disease: influence of _-galactosidase A activity and genetic mutations on clinical course. *Medicine (Baltimore)* 2002;81:122–138.
27. West M, Nicholls K, Mehta A, et al. Agalsidase alfa and kidney dysfunction in Fabry disease. *J Am Soc Nephrol* 2009;20:1132–1139.
28. Barbey F, Lidove O, Schwarting A. Fabry nephropathy: 5 years of enzyme replacement therapy—a short review. *Nephrol Dial Transplant* 2008;1:11–19.
29. Schiffmann R, Warnock DG, Banikazemi M, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol Dial Transplant* 2009;24:2102–2111.
30. Ortiz A, Oliveira JP, Waldek S, Warnock DG, Cianciaruso B, Wanner C, Fabry Registry. Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. *Nephrol Dial Transplant* 2008;23:1600–1607.
31. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest* 2004;34:236–242.
32. Germain DP, Waldek S, Banikazemi M, et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007;18:1547–1557.
33. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007;146:77–86.
34. Tahir H, Jackson LL, Warnock DG. Antiproteinuric therapy and Fabry nephropathy: sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-beta. *J Am Soc Nephrol* 2007;18:2609–2617.
35. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470.
36. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;58:259–263.
37. Tondel C, Ramaswami U, Aakre KM, Wijburg F, Bouwman M, Svarstad E. Monitoring renal function in children with Fabry disease: comparisons of measured and creatinine-based estimated glomerular filtration rate. *Nephrol Dial Transplant* 2010;25:1507–1513.
38. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;20:629–637.
39. Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM. Estimation of glomerular filtration rate from plasma creatinine concentration in children. *Arch Dis Child* 1976;51:875–878.
40. Levey AS. Clinical practice. Nondiabetic kidney disease. *N Engl J Med* 2002;347:1505–1511.
41. Strotmann J, Weidemann F, Breunig F, Knoll A, Wanner C, Ertl G. Morbus Fabry of the heart. Why should cardiologists care? *Z Kardiol* 2005;94:557–563.
42. Kampmann C, Linhart A, Baehner F, et al. Onset and progression of the Anderson-Fabry disease related cardiomyopathy. *Int J Cardiol* 2008;130:367–373.
43. Eng CM, Fletcher J, Wilcox WR, et al. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J Inherit Metab Dis* 2007;30:184–192.
44. Linhart A, Kampmann C, Zamorano JL, et al. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J* 2007;28:1228–1235.
45. Weidemann F, Strotmann JM, Niemann M, et al. Heart valve involvement in Fabry cardiomyopathy. *Ultrasound Med Biol* 2009;35:730–735.
46. Weidemann F, Niemann M, Breunig F, et al. Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. *Circulation* 2009;119:524–529.
47. Beer M, Weidemann F, Breunig F, et al. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. *Am J Cardiol* 2006;97:1515–1518.
48. Mehta A, Clarke JT, Giugliani R, et al. Natural course of Fabry disease: changing pattern of causes of death in FOS—Fabry Outcome Survey. *J Med Genet* 2009;46:548–552.
49. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. *Genet Med* 2009;11:790–796.
50. Hughes DA, Elliott PM, Shah J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomized, double-blind, placebo-controlled clinical trial of agalsidase-alfa. *Heart* 2008;94:153–158.
51. Kampmann C, Linhart A, Devereux RB, Schiffmann R. Effect of agalsidase alfa replacement therapy on Fabry disease-related hypertrophic cardiomyopathy: a 12- to 36-month, retrospective, blinded echocardiographic pooled analysis. *Clin Ther* 2009;31:1966–1976.
52. Mehta A, Beck M, Elliott P, et al. Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. *Lancet* 2009;374:1986–1996. [Erratum in: *Lancet* 2010;375:200.]
53. Pisani A, Spinelli L, Sabbatini M, et al. Enzyme replacement therapy in Fabry disease patients undergoing dialysis: effects on quality of life and organ involvement. *Am J Kidney Dis* 2005;46:120–127.
54. Kalliokoski RJ, Kantola I, Kalliokoski KK, et al. The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease. *J Inherit Metab Dis* 2006;29:112–118.

55. Elliott PM, Kindler H, Shah JS, et al. Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. *Heart* 2006;92:357–360.
56. Weidemann F, Breunig F, Beer M, et al. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. *Circulation* 2003;108:1299–1301.
57. Spinelli L, Pisani A, Sabbatini M, et al. Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. *Clin Genet* 2004;66:158–165.
58. Vedder AC, Breunig F, Donker-Koopman WE, et al. Treatment of Fabry disease with different dosing regimens of agalsidase: effects on antibody formation and GL-3. *Mol Genet Metab* 2008;94:319–325.
59. Breunig F, Weidemann F, Strotmann J, Knoll A, Wanner C. Clinical benefit of enzyme replacement therapy in Fabry disease. *Kidney Int* 2006;69: 1216–1221.
60. Imbriaco M, Pisani A, Spinelli L, et al. Effects of enzyme replacement therapy in patients with Anderson-Fabry disease: a prospective long term cardiac magnetic resonance imaging study. *Heart* 2009;95:1103–1107.
61. Weidemann F, Linhart A, Monserrat L, Strotmann J. Cardiac challenges in patients with Fabry disease. *Int J Cardiol* 2010;141:3–10.
62. Toro R, Perez-Isla L, Doxastaquis G, et al. Clinical usefulness of tissue Doppler imaging in predicting preclinical Fabry cardiomyopathy. *Int J Cardiol* 2009;132:38–44.
63. Sims K, Politei J, Banikazemi M, Lee P. Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry registry. *Stroke* 2009;40:788–794.
64. Rolfs A, Bottcher T, Zschiesche M, et al. Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. *Lancet* 2005;366: 1794–1796.
65. Brouns R, Sheorajpanday R, Braxel E, et al. Middelheim Fabry Study (MiFaS): a retrospective Belgian study on the prevalence of Fabry disease in young patients with cryptogenic stroke. *Clin Neurol Neurosurg* 2007; 109:479–484.
66. Wozniak MA, Kittner SJ, Tuhrim S, et al. Frequency of unrecognized Fabry disease among young European-American and African-American men with first ischemic stroke. *Stroke* 2010;41:78–81.
67. Kleinert J, Dehout F, Schwarting A, et al. Prevalence of uncontrolled hypertension in patients with Fabry disease. *Am J Hypertens* 2006;19:782–787.
68. Moore DF, Altarescu G, Herscovitch P, Schiffmann R. Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease. *BMC Neurol* 2002;2:4.
69. Moore DF, Altarescu G, Ling GS, et al. Elevated cerebral blood flow velocities in Fabry disease with reversal after enzyme replacement. *Stroke* 2002;33:525–531.
70. Moore DF, Altarescu G, Pursley R, et al. Arterial wall properties and Womersley flow in Fabry disease. *BMC Cardiovasc Disord* 2002;2:1.
71. Politei JM. Can we use statins to prevent stroke in Fabry disease? *J Inherit Metab Dis* 2009;32:481–487.
72. Hoffmann B, Beck M, Sunder-Plassmann G, Borsini W, Ricci R, Mehta A, FOS European Investigators. Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy—a retrospective analysis from the Fabry Outcome Survey. *Clin J Pain* 2007;23:535–542.
73. Ramaswami U, Wendt S, Pintos-Morell G, et al. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease. *Acta Paediatr* 2007;96:122–127.
74. Hopkin RJ, Bissler J, Banikazemi M, et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. *Pediatr Res* 2008; 64:550–555.
75. Pintos-Morell G, Beck M. Fabry disease in children and the effects of enzyme replacement treatment. *Eur J Pediatr* 2009;168:1355–1363.
76. Gibas AL, Klatt R, Johnson J, Clarke JT, Katz J. A survey of the pain experienced by males and females with Fabry disease. *Pain Res Manag* 2006;11:185–192.
77. MacDermot J, MacDermot KD. Neuropathic pain in Anderson-Fabry disease: pathology and therapeutic options. *Eur J Pharmacol* 2001;429:121–125.
78. Baehner F, Kampmann C, Whybra C, Miebach E, Wiethoff CM, Beck M. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. *J Inherit Metab Dis* 2003;26:617–627.
79. Schiffmann R, Kopp JB, Austin HA 3rd, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001;285:2743–2749.
80. Hoffmann B, Garcia de Lorenzo A, Mehta A, Beck M, Widmer U, Ricci R, FOS European Investigators. Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). *J Med Genet* 2005;42:247–252.
81. Eto Y, Ohashi T, Utsunomiya Y, et al. Enzyme replacement therapy in Japanese Fabry disease patients: the results of a phase 2 bridging study. *J Inherit Metab Dis* 2005;28:575–583.
82. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A—replacement therapy in Fabry's disease. *N Engl J Med* 2001;345:9–16.
83. Cleeland CS. Pain assessment: the advantages of using pain scales in lysosomal storage diseases. *Acta Paediatr Suppl* 2002;91:43–47.
84. Schiffmann R, Floeter MK, Dambrosia JM, et al. Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. *Muscle Nerve* 2003;28:703–710.
85. Lidove O, Ramaswami U, Jaussaud R, et al. Hyperhidrosis: a new and often early symptom in Fabry disease. International experience and data from the Fabry Outcome Survey. *Int J Clin Pract* 2006;60:1053–1059.
86. Peltier A, Smith AG, Russell JW, et al. Reliability of quantitative sudomotor axon reflex testing and quantitative sensory testing in neuropathy of impaired glucose regulation. *Muscle Nerve* 2009;39:529–535.
87. Hoffmann B, Schwarz M, Mehta A, Keshav S. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. *Clin Gastroenterol Hepatol* 2007;5:1447–1453.
88. Dehout F, Roland D, Treille de Granseigne S, Guillaume B, Van Maldergem L. Relief of gastrointestinal symptoms under enzyme replacement therapy in patients with Fabry disease. *J Inherit Metab Dis* 2004;27:499–505.
89. Banikazemi M, Ullman T, Desnick RJ. Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy. *Mol Genet Metab* 2005;85:255–259.
90. Wraith JE, Tylki-Szymanska A, Guffon N, et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. *J Pediatr* 2008;152: 563–570.
91. Hegemann S, Hajioff D, Conti G, et al. Hearing loss in Fabry disease: data from the Fabry Outcome Survey. *Eur J Clin Invest* 2006;36:654–662.
92. Hajioff D, Enever Y, Quiney R, Zuckerman J, Mackermot K, Mehta A. Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy. *J Inherit Metab Dis* 2003;26:787–794.
93. Hajioff D, Hegemannn S, Conti G, et al. Agalsidase alpha and hearing in Fabry disease: data from the Fabry Outcome Survey. *Eur J Clin Invest* 2006;36:663–667.
94. 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;65:299–307.
95. Giannini EH, Mehta AB, Hilz MJ, et al. A validated disease severity scoring system for Fabry disease. *Mol Genet Metab* 2010;99:283–290.
96. Weinreb NJ, Aggio MC, Andersson HC, et al. Gaucher disease type 1: revised recommendations on evaluations and monitoring for adult patients. *Semin Hematol* 2004;41:15–22.
97. Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. *Semin Hematol* 2004;41:4–14.
98. Charrow J, Andersson HC, Kaplan P, et al. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. *J Pediatr* 2004;144:112–120.
99. Pastores GM, Giraldo P, Cherin P, Mehta A. Goal-oriented therapy with miglustat in Gaucher disease. *Curr Med Res Opin* 2009;25:23–37.
100. Muenzer J, Wraith JE, Beck M, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). *Genet Med* 2006;8:465–473.
101. Martins AM, D'Almeida V, Kyosen SO, et al. Guidelines to diagnosis and monitoring of Fabry disease and review of treatment experiences. *J Pediatr* 2009;155:S19–S31.
102. Hughes DA, Ramaswami U, Elliot P, et al. Guidelines for the diagnosis and management of Anderson-Fabry disease. London, UK: National Commissioning Group of the National Health Service, 2005:1–37.
103. Clarke LA, Clarke JTR, Sirrs S, et al. Fabry disease: recommendations for diagnosis, management, and enzyme replacement therapy in Canada, 2005. Available at: http://www.garrod.ca/data/attachments/CanadianFabryGuidelinesNov05.pdf. Accessed September 9, 2010.
104. Lidove O, Bekri S, Goizet C, et al. [Fabry disease: proposed guidelines from a French expert group for its diagnosis, treatment and follow-up.] *Presse Med* 2007;36:1084–1097.

