Screening, diagnosis, and management of patients with Fabry disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference

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Patients with Fabry disease (FD) are at a high risk for developing chronic kidney disease and cardiovascular disease. The availability of specific but costly therapy has elevated the profile of this rare condition. This KDIGO conference addressed controversial areas in the diagnosis, screening, and management of FD, and included enzyme replacement therapy and nonspecific standard-of-care therapy for the various manifestations of FD. Despite marked advances in patient care and improved overall outlook, there is a need to better understand the pathogenesis of this glycosphingolipidosis and to determine the appropriate age to initiate therapy in all types of patients. The need to develop more effective specific therapies was also emphasized.


KEYWORDS: chronic kidney disease; enzyme replacement therapy; Fabry disease; Fabry nephropathy; standard of care

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Fabry disease (FD; OMIM entry number: 301500) is an X-linked lysosomal storage disorder caused by deficient activity of α-galactosidase A resulting in accumulation of glycosphingolipids with terminal α-D-galactosyl residue, particularly globotriaosylceramide (GL-3, Gb3, CTH) and globotriaosylsphingosine (Lyso-GL-3, lyso-Gb3). These lipids progressively accumulate in the circulation and in virtually all cell types and organs, resulting in the development of a multisystem disorder. Affected patients are at high risk of developing a small-fiber neuropathy, progressive proteinuric kidney disease, fibrotic cardiac disease resulting in rhythm and conduction disturbances, progressive hypertrophic cardiomyopathy, and mostly ischemic cerebrovascular stroke. Although this disease is X-linked, both males and females are affected by it.

Although diagnosis and management of FD have markedly improved over the years, the disease has no cure, and current therapy is suboptimal. Our goal was to summarize the current knowledge and knowledge gaps regarding screening, diagnosis, and therapy, and to propose a research agenda to resolve outstanding controversial issues.

SCREENING AND DIAGNOSIS
Clinical presentation and diagnostic testing
The clinical characteristics of FD are described in Table 1. The diagnosis is established in males by α-galactosidase A–specific activity that is below 25% to 30% of mean control in peripheral white blood cells.2,4–7 Alpha-galactosidase A activity is somewhat predictive of classic or later-onset manifestations. Classically affected hemizygotes have undetectable or very low (≤3%) enzymatic activity.2 As with many genetic diseases, there is a wide phenotypic variability even among patients with the same GLA mutation. A late-onset phenotype of FD exists mainly with cardiac-variant disease forms.9 These patients present with typical disease in their fifth or sixth decade but often lack the early alerting clinical features of angio-keratoma, acroparesthesia, corneal opacities, and sweating abnormalities. Patients with milder variants typically have
missense GLA mutations and variable residual enzyme activity. For example, the N215S mutation may have residual enzyme activity in plasma and/or leucocytes close to the normal range. One exception is a splice mutation common in Taiwanese patients with FD who have 10% residual enzyme activity and develop left ventricular hypertrophy in their fourth or fifth decade of life.

In heterozygous females, random X-inactivation may result in expression of α-galactosidase A activity in the plasma or leucocytes within the normal range in up to 60% of women. Sequencing of the GLA gene is necessary for a diagnosis of FD in most females. In addition to point mutations, frameshift mutations and small deletions within exons and exon-intron boundaries, large deletions, and intronic mutations have been described. The finding of elevated globotriaosylceramide (Gb3) in relevant tissues should be the ultimate requirement when confronted with GLA variants of unknown significance. Erroneous attribution of pathogenicity to a mutation may lead to a costly and inappropriate use of specific therapy such as enzyme replacement therapy (ERT) and a missed opportunity to make the correct diagnosis. Where enzyme activity is low and no mutation is found by Sanger sequencing of exons and exon-intron boundaries, further investigations including multiplex ligation-dependent probe amplification analysis and assessment of specific intronic mutations should be performed.

Substrate accumulation including Gb3 and lyso-Gb3 may occur in plasma and urine. While glycolipid urinalysis may be helpful in attributing pathogenicity or phenotype, it may be less useful in screening because increased urinary Gb3 has been described in cohorts of patients with cardiac disease or nephrotic syndrome without a diagnosis of FD.

### Screening strategies for Fabry disease

Based on recent newborn screening studies each including at least 30,000 newborns, the prevalence of FD was found to be markedly higher than previously expected with 1 in 3100 males reported in northwestern Italy, 1 in 3000 males in Austria, 1 in 1300 males in Taiwan, 1 in 7800 males in Washington state (USA), and 1 in 1500 males in Missouri (USA). Before these studies, the prevalence was expected to be much lower: 1 in 117,000 in Australia, 1 in 468,000 in the Netherlands, and only 1 in 833,000 in Portugal. High-risk screening. Screening for stroke in the young has shown definite FD in 0.5%, in 0.9% of the hypertensive population with left ventricular hypertrophy, in 0.5% to 1% of patients with idiopathic hypertrophic cardiomyopathy, but 4% of males, and in 0.11% to 0.17% of dialysis patients. Only 0.2% of unselected patients with common heart disease have FD. Prevalence screening studies may inadvertently indicate falsely higher prevalence due to benign polymorphisms (e.g., D313Y).

FD should be considered and tested in patients with chronic kidney disease (CKD) with no definitive cause of nephropathy and when no biopsy has been performed, especially in familial cases. The difficulty in recognizing this condition due to a highly variable and nonspecific phenotype, lack of positive family history in at least 5% of cases, and a low prevalence rate in many regions of the world signifies that many patients are diagnosed late or never diagnosed. This situation can only be reversed by the introduction of widespread screening of at-risk patients.

**Family screening.** The X-linked nature of FD inheritance renders cascade screening of families efficient and of high diagnostic yield over on average 3 generations surrounding an index case. All index patients should meet with a genetic counselor or a physician to produce an informative family tree and facilitate communication with predicted affected family members so they may be referred to a medical geneticist for genetic counseling and testing. Considering the privacy of the index case is important and must be weighed against the risk of delayed diagnosis in family members.

Many patients find it valuable to discuss implications of testing with a clinical geneticist and may wish to consider preconception genetic diagnosis, prenatal testing, or postnatal

### Table 1 | Manifestations in Fabry disease

| Childhood and adolescence (≤16 years) | Acroparesthesia/pain crisis: chronic or episodic, burning sensation in the palms of hands or soles of feet, exacerbated by temperature changes, fever, stress, physical exercise, and alcohol |
| | Angiokeratomas: small, raised, dark red spots that develop slowly and can be found on the buttocks, genitalia, inner thighs, back, and oral cavity |
| | Ophthalmologic abnormalities: cornea verticillata (whorl-shaped opacity), posterior subcapsular cataracts, tortuous vascular lesions in the retina and conjunctiva, dilated vessels on upper lid margin |
| | Sensorineural hearing loss |
| | Hypohidrosis or anhidrosis |
| | Increased albuminuria |
| | History of nonspecific bowel disturbances |
| | History of lethargy and fatigue |
| Early adulthood (17–30 years) | More extensive angiokeratomas |
| | High albuminuria (≥1g/24 hours) |
| | Edema or lymphedema |
| | Fever |
| | Hypohidrosis or anhidrosis |
| | Lympadenopathy |
| | Heat sensitivity |
| | Diarrhea, abdominal pain |
| | Cardiac: bradycardia, short PR interval, left ventricular hypertrophy, conduction defects |
| Later adulthood (age > 30 years) | Heart disease: fibrotic, left and right ventricular hypertrophy, heart valve abnormalities and dysrhythmias, sudden cardiac death, angina, diastolic heart failure, cardiac transplantation |
| | Chronic kidney disease: including end-stage renal disease requiring renal replacement therapy with dialysis or renal transplantation |
| | Stroke or transient ischemic attacks |
| | Deafness, of acute or chronic onset |
diagnosis. Diagnosis in a Fabry male has particular diagnostic implications for his mother and daughters, who will all, in the absence of new mutations or nonpaternity, have positive test results. The risk of FD in any male or female offspring of a woman with FD is 50%.27 Once a genetic diagnosis has been made, patients should undergo a full clinical evaluation and treatment as described in Supplementary Table S1.

**Knowledge gaps and research recommendations** *(Table 2).* The true prevalence of FD is not known, but future systematic screening for the disease in the general population may help determine it. Another challenge is to predict the pathogenicity of some GLA variants. Because newborn screening for FD has effectively begun in certain jurisdictions, future research must evaluate the ethical and psychological ramifications of early diagnosis of a disorder that may or may not manifest itself until years or decades later.

**ENZYME REPLACEMENT THERAPY**
ERT with recombinant human α-galactosidase A (agalsidase) is the only currently available therapy aimed at the etiology of FD *(Supplementary Table S2).* Agalsidase-α and agalsidase-β have been studied in clinical trials with different primary endpoints, hampering comparison of effectiveness. However, surrogate endpoints were evaluated on both enzymes in placebo-controlled trials that led to regulatory approval *(Supplementary Table S3).* These trials have reported on short periods of ERT, with different clinical endpoints, predominantly in (male) typical patients. As FD is a rare chronic, slowly progressive disease with a 4-decade natural history and broad heterogeneous presentation, this evidence is incomplete. Extrapolating results to long-term patient management or other Fabry populations is challenging. Based on ethical and feasibility considerations, it is very unlikely that further evidence from placebo-controlled trials will become available. Additional knowledge is provided by case series and post-marketing surveillance databases that, despite their limitations, suggest that the earlier therapy is started, the better the outcome may be. This observation is in accordance with the hypothesis that glycolipid clearance is most therapeutically effective before secondary, irreversible tissue injury has occurred.

**Initiation of ERT**
Expert opinion-based recommendations on initiation and cessation of ERT are available.28,29 However, there is no scientific evidence as to the optimal age of ERT initiation. Therefore, there are no uniform guidelines, and conditions and age to start ERT differ in various countries. In general, development of signs or symptoms related to FD is an indication to start ERT. For the kidney, this implies the development of CKD (i.e., pathological albuminuria or decreased glomerular filtration rate [GFR]) or progressive decrease in GFR if ERT has not already been started earlier for nonrenal manifestations such as pain.30 The benefits of early treatment, before irreversible tissue injury occurs, should be balanced against the burden of biweekly infusions in very young individuals. In a recent pediatric randomized controlled trial (RCT), Fabry arteriopathy and segmental effacement of podocyte foot processes were found in all biopsied FD patients with normal GFR and urinary albumin-to-creatinine ratio (UACR) < 30 mg/g,31 suggesting early

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ERT, enzyme replacement therapy; FD, Fabry disease.
renal involvement and by inference an indication for initia-
tion of ERT before kidney injury, marked by proteinuria or
reduced GFR, become clinically apparent. There is lack of
agreement on cessation criteria.

Glycolipid deposits. Placebo-controlled RCTs in classic FD
have consistently shown that within 6 months, ERT reduces
plasma and urinary Gb3 and capillary endothelial Gb3
(Supplementary Table S3). Clearance of Gb3 in other slowly
dividing cells may take years. In young patients, there is some
limited evidence of a dose-dependent clearance of podocytes
over 5 years of follow-up.32 This finding has not yet been
established as an acceptable surrogate for beneficial renal
therapeutic effect.

Kidney, cardiac, and cerebral disease. Overall, there is a
suggestion that ERT slows the progression of kidney
involvement in FD and results in reduction of hypertrophic
cardiomyopathy, especially when started prior to established
fibrosis. However, there is no reduction in the rate of stroke
with ERT. Though there are limited data and only few
comparative studies, it is suggested that dose may have an
impact. Only 1 placebo-controlled study addressed the effec-
t of ERT (1.0 mg/kg/2 weeks agalsidase-β) on severe renal,
cardiac, or central nervous system events. A small decrease in
clinical events was observed after a prespecified correction for
imbalances at baseline (Supplementary Table S3).33 One
patient registry study shows a decline in clinical event rate
after the first 6 months of agalsidase-β, but in general there is
no indication that the event rate on ERT is lower than the
natural history of the disease.34–35 The clinical event rate for
patients taking agalsidase-α has not been published, although
morbidity may be delayed in these patients.36 The observed
differences in ERT outcomes may be caused by the profound
clinical heterogeneity of studied patients (Supplementary
Table S3).

Proteinuria is a well-recognized factor associated with
progressive loss of kidney function in many forms of CKD.37
In the phase 3 trial with agalsidase-β, classic FD patients
presenting with <1.0 g/day (d) of proteinuria had stabili-
zation of their renal function during 5 years of follow-up.38 In
contrast, classic patients presenting with >1 g/d of protein-
uria, usually associated with fibrosis and scarring in more
than half of the glomeruli on baseline renal biopsies, had
progressive loss of kidney function, many reaching CKD stage
5.39 These results have been extended with 10 years of follow-
up. The important factors related to progressive loss of kidney
function were age at which ERT was initiated and averaged
ratio of urinary protein to creatinine <0.5 g/g (<0.5 g/d, <50
mg/mmol) during the follow-up period.39,40 In those with
uncontrolled proteinuria or a reduced GFR (<60 ml/min/
1.73 m²), ERT alone does not seem to prevent further de-
teriation of renal function.

The phase 3 follow-up results have been incorporated into
various treatment recommendations, with the suggestion that
ERT be withheld if there is clinical evidence of more severe
renal involvement as denoted by significant proteinuria or
loss of kidney function. This recommendation does not
address the appreciable number of patients with FD who
present with pathological levels of albuminuria (≥30 mg/g
albumin-to-creatinine ratio) and reduced kidney function at
initial evaluation,41 or the opportunity to initiate ERT before
overt organ damage develops.32,42,43 Renal biopsies are useful
in such cases to determine the severity of cellular injury (e.g.,
podocyte effacement) and organ damage (e.g., glomerular
sclerosis and fibrosis; vascular smooth muscle hypertrophy
and arteriopathy) that can develop before clinical signs of
kidney involvement become apparent.

ERT may improve left ventricular hypertrophy if no
fibrosis is present at baseline,44,45 but cardiac fibrosis will
progress during ERT, especially if severe (i.e., greater than 3
segments). Left ventricular hypertrophy reduction is not a
proven surrogate for improved cardiovascular outcome.
There is no evidence of reversal or prevention of electrocardi-
ogram changes or clinical arrhythmia. In the absence of a
proper control group, it is unknown whether the rate of
deterioration is slowed in those patients with most advanced
disease who continue to decline during ERT. Indeed,
cardiac death is a more common cause of death in patients
with FD than progression to end-stage renal disease.46,47

It is estimated that, depending on the age-range cohort, FD
patients have a 5.5- to 12.2-fold increased risk of stroke
compared to the general population.48 Strokes continue to
occur in patients on ERT.39,49,50 A long-term study from the
UK suggested that stroke occurred more often among patients
older than late 40s undergoing ERT.49 In that study, 19 of 212
patients who were undergoing ERT developed stroke or
transient ischemic attacks, while only 1 of 76 who were not
undergoing ERT developed such complications (P = 0.01,
Fisher’s exact test), possibly suggesting that those patients
with more severe manifestations were receiving ERT. In a
placebo controlled RCT, 2 of 31 patients (6.45%) in the
agalsidase-β group experienced a stroke.33 Post hoc analysis of this trial
suggested prevention of new white matter lesions following
ERT compared to placebo.51

Other symptoms. In placebo-controlled RCTs, both agal-
sidase-α and agalsidase-β improved pain scores in adults,52,53
but improvement was also seen in the placebo groups. In
general clinical experience, ERT is only mildly effective at
best in decreasing pain, and younger patients may respond
better than do older patients. Improved school attendance has
been reported with ERT.34–36 Patient-reported outcomes from
registry studies suggest improvement of quality of life (QoL)
with ERT. However, the outcome of QoL on ERT is
inconclusive.62
**The issue of dose.** The issue of dose has been confounded by the fact that the label-recommended dose of the 2 available agalsidase preparations has a 5-fold difference; thus, any discussion on dose must be interpreted in the context of the different enzyme preparations. In the absence of adequately powered RCTs directly comparing 0.2 to 1.0 mg/kg/2 weeks, individual physicians should evaluate the available placebo-controlled RCT, case-series, and Canadian FD Initiative clinical trial results for personalized decision-making (Supplementary Table S3).

A dose effect, at least in some patients, is suggested for podocyte Gb3 clearance and preservation of renal function in case series of repeat kidney biopsy in young patients. Doubling the frequency of 0.2 mg/kg agalsidase-α in patients with progressive kidney disease from biweekly to weekly is also suggested. The largest randomized, prospective head-to-head trial comparing agalsidase-α to agalsidase-β in adults is underpowered but has 5-year longitudinal data on 1.0 mg/kg/2 weeks agalsidase-β versus 0.2 mg/kg/2 weeks agalsidase-α with a primary outcome of severe clinical events. There was no significant difference in the event-free survival between the 2 treatment arms. While the hazard ratio of 1.46 favored agalsidase-β, perhaps reflecting differences in baseline characteristics among the 2 patient groups, a more recent analysis of the 8-year data (presented at the Society for the Study of Inborn Errors of Metabolism meeting in September 2016) reports a hazard ratio of 1.17, which again is not statistically significant despite a patient sample size of 115. While there is some evidence that higher agalsidase dose results in better biochemical clearance, at present there is no evidence to base treatment decisions on biomarker levels that do not correlate with patient outcomes.

The limited effect of ERT is likely due to a combination of: (i) delayed treatment initiation after the onset of irreversible organ damage; (ii) intermittent administration leaving the patient with little functional enzyme every second week; (iii) incomplete tissue penetration of the infused protein; (iv) presence of anti-agalsidase antibodies; (v) lack of appropriately powered RCTs to detect a very small clinical effect; and (vi) incompletely understood mechanism of response to ERT. Weekly infusions, a novel α-galactosidase A preparation with a longer half-life, or the use of small molecules, such as pharmacological chaperones or substrate synthesis reduction, may address some of these limitations.

**Follow-up of treatment.** Follow-up recommendations are listed in Supplementary Table S1. Patients with FD should have access to coordinated care through expert designated centers, either through their local physician or by visiting such a center.

Antibodies develop in a substantial proportion of typical male FD patients and also in some females, and negatively influence known substrate-related biomarkers. Gb3 accumulation in skin biopsies and greater disease progression were noted in patients with high antibody titers.

**Knowledge gaps and research recommendations (Table 2).** We do not know when ERT should be initiated and in particular at what age. Is there a cut-off age or disease stage beyond which benefit of ERT is minimal? These may be different for different organ systems. The net effect of ERT in females could also be better ascertained in clinical trials performed only in female FD patients.

**NONSPECIFIC STANDARD OF CARE THERAPY**

**Cardiac and cerebrovascular disease: heart failure, coronary disease, arrhythmia, and stroke**

Cardiac deaths account for the majority of deaths in FD in both sexes, and cardiomyopathy has been reported in up to 90% of patients. Low blood pressure is typical. Heart failure may have multifactorial causes that need to be treated according to general principles beyond ERT. Many patients do not tolerate β-blockers and may need a pacemaker due to bradycardia. Adjunctive treatment of the cardiac disease includes renin angiotensin system blockers, which in general have beneficial effects on regression of hypertrophy. The beneficial effect of these drugs is especially well documented when there is concomitant CKD and hypertension. While chest pain and dyspnea may pose a diagnostic challenge, coronary disease should be diagnosed and treated similarly to treatment in non-FD patients.

Cardiac arrhythmias and conduction abnormalities are frequent, and bradycardia and atrial fibrillation are common findings. The risk of stroke in patients with paroxysmal atrial fibrillation, which is often asymptomatic, may be underestimated, and anticoagulation is needed in many of these patients. The indication is probably stronger than the general recommendations in the ESC guidelines, although the risk for cerebral microbleeds must be recognized. Because both small and large cerebral vessels are involved, effective antiplatelet agents are highly recommended to prevent stroke in enzyme-naïve patients and in those undergoing ERT for primary and secondary stroke prevention. Implantation of a pacemaker is necessary in cases with symptomatic and severe bradycardia. Malignant arrhythmias are usually associated with occurrence of replacement fibrosis in advanced hypertrophic cardiomyopathy in male patients, and may also be seen in females before they develop overt left ventricular hypertrophy. Implantation of a cardioverter-defibrillator should be considered in these patients.

**Pulmonary disease**

Dyspnea is a frequent symptom in many patients, and differential diagnosis between disturbed systolic or diastolic cardiac function versus pulmonary or airway dysfunction may be difficult. A mixture of different etiologic mechanisms of obstructive and restrictive pulmonary symptoms has been reported in several small studies and case reports, and a recent systematic review could not identify consistent findings in the literature. A registry study concluded that 23 of 67 patients had airway obstruction similar to chronic obstructive pulmonary disease, and obstructive lung disease has been...
reported to be up to 10 times more prevalent in people with FD than in the general population.

Neuropathic pain (chronic pain and pain crisis)

Neuropathic pain associated with small fiber neuropathy is a key feature of FD from childhood or early adulthood (average age of onset is 9 years in males and 16 years in females, though onset as early as the age of 5 years has been reported).87,88 No RCT has been conducted in the treatment of neuropathic pain in FD. Tables 3 and 4 show recommended approaches to treatment of chronic neuropathic pain and pain crisis in FD.

The mechanisms of FD neuropathy are not fully understood, but evidence of substrate deposits in dorsal root ganglia, stenosis and occlusion of vasa nervorum, and up-regulation of ectopic and unstable sodium channels and TRPV channels as expressions of nerve damage have been hypothesized to contribute to acroparesthesias and pain crises.89 Drugs generally have similar efficacy in various conditions, except in trigeminal neuralgia, chronic radiculopathy, and HIV neuropathy, with level A evidence in support of tricyclic antidepressants, pregabalin, gabapentin, tramadol, and opioids (in various conditions) and duloxetine, venlafaxine, topical lidocaine, and capsaicin patches (in restricted conditions). Combination therapy appears useful for tricyclic antidepressants, gabapentin, and gabapentin-opioids.90 Sodium-channel blockers (carbamazepine) have been reported to have beneficial effect on gastrointestinal symptoms as well as emotional (depressive) symptoms.91,92

Renal involvement

Gb3 deposits have been described in many renal cell types as early as 17 weeks of gestation93 and in placental tissue of patients with FD.94 Kidney biopsy studies have shown age-dependent progressive accumulation of Gb3 in podocytes, and correlations between early kidney damage and albuminuria.95 Early treatment with ERT may help prevent progressive renal involvement during 5 years of treatment in children with normoalbuminuria or microalbuminuria.96 A correlation between the cumulative administered dose of ERT, podocyte clearance of Gb3, and improvement in albuminuria has been suggested.96 Importantly, the transition from Gb3 accumulation in podocytes to the earliest phases of injury denoted by podocyte foot process effacement occurs before there are clinically evident increases in urinary albumin or protein excretion.42 Recently, increased urinary loss of podocytes has been described early in FD, again before the onset of clinically apparent proteinuria.43,96 The phases of tissue accumulation of Gb3, cellular injury, organ damage, and progressive loss of kidney function are represented in Figure 1.

Generally, the diagnosis of early decline of GFR in patients with FD and CKD is hampered by inaccuracy of creatinine-based GFR measurements. Overestimation of true GFR may be especially relevant in many male FD patients. A measured GFR (e.g., iohexol GFR) may therefore be helpful in the assessment of nephropathy.97,98 However, it should be emphasized that there may be significant renal involvement before any changes in GFR are measured or estimated (Figure 1).

The mainstay approach for reducing urinary protein and albumin excretion in all forms of CKD has been the use of renin angiotensin system blockade with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, which has also been associated with improved renal and cardiac outcomes.99 Recognizing the trade-off of control of proteinuria and the associated reduction in blood pressure with these agents, the goal for proteinuria reduction is not clearly defined in any form of CKD. The best available evidence is based on a meta-analysis of nondiabetic CKD treated with angiotensin-converting enzyme inhibitors; there was a clear-cut benefit of ACE inhibition compared to other forms of hypertension control when urinary protein excretion exceeded 500 mg/d.99 Renin angiotensin system blockade has been shown to prevent the transition from microalbuminuria to overt albuminuria in patients with diabetes, but this effect was reversed when the therapy was stopped and did not have a persistent beneficial effect on kidney function.100–102 The effects of angiotensin-receptor blocker therapy on albumin excretion can be dissociated from the primary effect on systemic blood pressure, and in post hoc analyses, changes in urinary albumin excretion have been independently associated with slowing of progressive loss of renal function.103 Despite these promising findings, more recent efforts to prevent microalbuminuria or aggressively control proteinuria in diabetic kidney disease have been disappointing.104

There is a direct relationship between loss of renal function and sex, and also with severity of proteinuria both before and after the initiation of ERT.105–107 A single-center study reported stabilization of renal function in 6 classic FD patients at high risk for progression to end-stage renal disease.

| Table 3 | Adjunctive therapy for chronic pain |
| --- | --- | --- | --- |
| Agent | Dose range | Cardiac restrictions | Renal restrictions |
| Carbamazepine115,116 | 250–800 mg/d | May interfere with activity of other drugs (e.g., warfarin) | None |
| Gabapentin117 | Slowly titrated from 100 to a max of 2400 mg/d | None | Caution with chronic kidney disease |
| Phenytoin118 | 300 mg/d | None | Caution with chronic kidney disease |
| Pregabalin119 | 75–300 mg/d | None | None |
| Tricyclic antidepressants119 | 25–150 mg/d | Arrhythmias | None |
| Duloxetine120 | 60–120 mg /d | None | None |
Table 4 | Adjunctive therapy for pain crisis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose range</th>
<th>Experience in Fabry disease and side effects</th>
<th>Cardiac and renal restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV lidocaine</td>
<td>2–5 mg/kg</td>
<td>Good clinical response</td>
<td>Arrhythmias, no renal restrictions</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100–400 mg/d</td>
<td>Caution with concomitant use of SSRI, SNRI, TCA</td>
<td>Caution with chronic kidney disease and epilepsy</td>
</tr>
<tr>
<td>Morphine</td>
<td>Titration of 30–120 mg every 12 h</td>
<td>Monitor for addiction; constipation</td>
<td>None</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Titration of 20–60 mg every 12 h</td>
<td>Monitor for addiction; constipation</td>
<td>None</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50–150 mg/d</td>
<td>Risk of GI bleeding</td>
<td>Caution with chronic kidney disease</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; h, hours; IV, intravenous; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

with control of proteinuria to a target of 0.5 g/d while receiving concurrent ERT at 1 mg/kg every 2 weeks. This study was recognized in the European Renal Best Practice report, but was not incorporated into the overall recommendations pending confirmation of these findings in a larger group of classic FD patients. A recent report on a larger series of 24 patients described successful titration and maintenance of urinary protein-to-creatinine ratio at 0.5 g/g with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers in 18 of the 24 patients who completed the 24-month open-label protocol. Despite successful control of proteinuria in these 18 patients, only 6 experienced stabilization of their kidney function, while the remaining 12 patients continued to lose renal function at the same rate as the 6 patients who could not achieve the target for control of proteinuria. The only identified factor that distinguished the patients who achieved the proteinuria goal and had preserved renal function from those who did not have preserved renal function was the age at which ERT was initiated. Similarly, a 10-year follow-up of the phase 3 agalsidase-β trial patients showed that those who started ERT at a younger age had a significantly more favorable response.

Individual FD patients should follow the general guidelines for management of CKD, including blood pressure optimization, smoking cessation, dietary salt restriction, and management of hyperlipidemia. A kidney biopsy should definitely be considered to confirm the diagnosis of Fabry nephropathy, evaluate the severity of irreversible renal involvement, and diagnose superimposed kidney disease in cases of unexpected kidney findings. Several other approaches have also been described, including decreasing the ERT dosing interval, the addition of amiloride to the anti-proteinuric regimen, and the addition of paricalciotol therapy to renin angiotensin system blockade. Prospective evaluations of these approaches with larger numbers of patients are needed to improve the renal outcomes of patients with FD.

Knowledge gaps and research recommendations (Table 2). The biggest challenge is to separate the net contribution of specific therapy such as ERT from the overall effect of the nonspecific but powerful standard of care interventions described above. Future research should focus on additional ways to protect the glomerular function of the kidneys and cardiac rhythm and conduction system. The latter has thus far not responded to any specific treatment.

CONCLUSION

FD is a complex multisystem disease with mostly nonspecific symptoms and signs. Diagnosis requires a high index of suspicion in symptomatic patients and screening of certain at-risk groups. Common standard-of-care therapies are highly effective in alleviating symptoms and treating disease complications. ERT is the first specific therapy developed that can slow kidney disease and alleviate symptoms but confers little benefit to cardiovascular and cerebrovascular outcomes. Additional specific therapeutic agents such as modified ζ-galactosidase A with a longer half-life and better tissue penetration, pharmacological chaperones, and substrate reduction therapy may further improve patient health.

DISCLOSURE

RS declared having received consultancy fees from Protalix (monies went to Baylor Research Institute), speaker honoraria from Sanofi Genzyme, and research support from Protalix. DAH declared having received consultancy fees from Amicus, Genzyme, Protalix and Shire; speaker honoraria from Genzyme and Shire; and research support from Shire. GEL declared having received travel support, consultancy

Figure 1 | Fabry nephropathy: GL3 accumulation, cellular injury, organ injury, and progressive loss of renal function. Adapted from Eng et al. with permission. ACR, albumin-creatinine ratio; ESRD, end-stage renal disease; GFR, glomerular filtration rate.
fees, and educational grants from Actelion, Amicus, Protalix, Sanofi Genzyme, and Shire HGT; all financial arrangements are made through GEL’s academic institution (AMC Medical Research BV). AO declared having received consultancy fees from Sanofi Genzyme; speaker honoraria from Sanofi Genzyme and Shire; and research support from Healthcare research fund (FIS, Spanish Government). ES declared having received consultancy fees from Genzyme and speaker honoraria from Genzyme and Shire. DGW declared having received consultancy fees from Actelion, Amicus, Genzyme and Protalix; and research support from the National Institutes of Health. MLW declared having received consultancy fees from Sanofi Genzyme; speaker honoraria from Excelsior Pharma, Sanofi Genzyme, and Shire; and research support from Sanofi Genzyme (Canada) and Shire. MLW has also served as an independent medical expert for medical legal cases. CW declared having received consultancy fees from Actelion and Sanofi Genzyme; speaker honoraria from Actelion and Sanofi Genzyme; and research support from Sanofi Genzyme.

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SUPPLEMENTARY MATERIAL
Table S1. Follow-up recommendations.
Table S2. Agalsidase preparations.
Table S3. Key phase 2 through phase 4 placebo-controlled agalsidase trials.
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES


APPENDIX

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