European expert consensus statement on therapeutic goals in Fabry disease

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Abstract

Background

Fabry disease, an inherited lysosomal storage disorder, causes multi-organ pathology resulting in substantial morbidity and a reduced life expectancy. Although Fabry disease is an X-linked disorder, both genders may be affected, but generally to a lesser extent in females. The disease spectrum ranges from classic early-onset disease to non-classic later-onset phenotypes, with complications occurring in multiple organs or being confined to a single organ system depending on the stage of the disease. The impact of therapy depends upon patient- and disease-specific factors and timing of initiation.

Methods

A European panel of experts collaborated to develop a set of organ-specific therapeutic goals for Fabry disease, based on evidence identified in a recent systematic literature review and consensus opinion.

Results

A series of organ-specific treatment goals were developed. For each organ system, optimal treatment strategies accounted for inter-patient differences in disease severity, natural history, and treatment responses as well as the negative burden of therapy and the importance of multidisciplinary care. The consensus therapeutic goals and proposed patient management algorithm take into account the need for early disease-specific therapy to delay or slow the progression of disease as well as non-specific adjunctive therapies that prevent or treat the effects of organ damage on quality of life and long-term prognosis.

Conclusions

These consensus recommendations help advance Fabry disease management by considering the balance between anticipated clinical benefits and potential therapy-related challenges in order to facilitate individualized treatment, optimize patient care and improve quality of life.

Keywords: Fabry disease, therapeutic goal, disease management, consensus, enzyme replacement therapy
Highlights

- Therapeutic goals for patients with Fabry disease should be individualized by considering the patient characteristics, disease variant and stage.
- The reversal of symptoms or prevention of disease progression is the goal for most parameters associated with Fabry disease.
- Multidisciplinary input is vital at all stages of Fabry disease management and should be based on a comprehensive assessment of affected organs and regular monitoring.
- Timing of therapy plays an important role in Fabry disease management; early initiation of disease-specific therapy can delay progression in patients with Fabry disease.
- Optimal Fabry disease management includes both disease-specific and adjunctive treatment and should consider the balance between anticipated clinical benefits and potential therapy-related challenges.
List of abbreviations

ACEi  angiotensin-converting enzyme inhibitor
ARB  angiotensin II receptor blocker
BPI  Brief Pain Inventory
CKD  chronic kidney disease
CNS  central nervous system
ECG  electrocardiogram
eGFR  estimated glomerular filtration rate
EOW  every other week
ERT  enzyme replacement therapy
ESKD  end-stage kidney disease
EQ-5D  EuroQoL 5 Dimensions questionnaire
FOS  Fabry Outcome Survey
GFR  glomerular filtration rate
GL-3  globotriaosylceramide
GSRS  Gastrointestinal Symptom Rating Scale
lyso-GL-3  globotriaosylsphingosine
LV  left ventricular
LVH  left ventricular hypertrophy
LVM  left ventricular mass
MRI  magnetic resonance imaging
PNS  peripheral nervous system
QoL  quality of life
SF-36  Short Form Health Survey
1. Introduction

Fabry disease (OMIM #301500) is an X-linked genetic disorder caused by a mutation in the GLA gene (OMIM #300644; HGNC:4296) resulting in a lysosomal enzyme deficiency of the acid hydrolase α-galactosidase. This deficiency results in progressive accumulation of globotriaosylceramides (GL-3) and its deacylated derivative globotriaosylsphingosine (lyso-GL-3) in the affected cells of damaged tissues and in body fluids. The tissue damage that is associated with GL-3 and lyso-GL-3 accumulation leads to the manifestations of Fabry disease in many organ systems including the heart, kidney and nervous system [1]. Early signs and symptoms usually manifest during childhood and adolescence in patients with the severe, classic form of Fabry disease, and may include neuropathic pain, autonomic dysfunction, gastrointestinal (GI) complaints, angiokeratomas, and hypohidrosis. These precede the development of kidney dysfunction, and cardiac and cerebrovascular complications in adulthood, which cause poor quality of life and an increased risk of premature death [1]. The age of onset of symptoms, the extent of organ involvement, and prognosis of Fabry disease depend on the underlying degree of α-galactosidase deficiency and – due to the X-linked nature of the disease and X-chromosome inactivation – on patient gender. Specifically, men with higher residual enzyme activity tend to have predominantly single organ forms of the disease of later adult onset and women tend to have milder disease phenotypes than men. Although the pathogenesis of Fabry disease is incompletely understood, ischemic tissue injury consequent to the accumulation of GL-3 in vascular endothelia, particularly of small vessels, is regarded as a distinguishing feature of the disease and a major therapeutic target evidenced by histopathology [1]. Furthermore, the proinflammatory role of GL-3 has been suggested to play a significant role in the underlying pathology of Fabry disease [2].

As Fabry disease causes tissue damage in a number of organ systems, the therapeutic approach to patients with Fabry disease should ideally be multidisciplinary and integrated into a comprehensive medical care plan that addresses individual patient health needs. As with other inborn errors of metabolism, such as Gaucher disease, mucopolysaccharidoses, and Pompe disease, there are several primary Fabry-specific therapies. Enzyme replacement therapy (ERT) has been approved for clinical use since 2001. Other therapies, including chaperone therapy, substrate reduction therapy and gene therapy have only recently been approved, are undergoing clinical trials, or are still in development. Patients with Fabry disease often also receive adjunctive therapies for complications such as chronic kidney disease (CKD), cardiac or neurological involvement. However, manifestations of Fabry disease often vary in different patients; therefore, therapeutic goals need to be individualized. Furthermore, as our understanding of Fabry disease improves and treatment...
options expand, it is important to regularly re-evaluate and appraise the therapeutic goals for patients with Fabry disease.

2. Methods

A European panel of experts was established with the objective of developing a set of detailed, organ-specific therapeutic goals for Fabry disease based on expert consensus and a systematic literature review that included articles published up to and including January 2017 [3–6]. The development of the therapeutic goals was guided by a number of key questions (Box):

1. What are the relevant clinical parameters that should be considered?
2. What is a reasonable response to therapy, and how should this be tailored to patient characteristics and disease severity?
3. What is demonstrated by published evidence and what can the clinical experience of the expert panel add to this information?
4. What are the unmet needs and gaps in clinical evidence that impede the identification of a reasonable therapeutic goal?

The systematic literature review and the meetings of the European expert panel were sponsored by Sanofi Genzyme. This paper presents the consensus reached on therapeutic goals drafted by specialist working groups, tasked with developing therapeutic goals for the heart, kidney, and nervous system in addition to an overall consensus on the goals for treatment of other organ manifestations of Fabry disease.

3. Metabolic biomarkers of Fabry disease in plasma and urine

3.1 Plasma GL-3

Plasma GL-3 is the most widely available indicator of glycosphingolipid load in patients with Fabry disease, although it must be noted that because of their heterozygosity for Fabry mutations and their X-chromosome inactivation patterns, the majority of female patients have normal plasma GL-3 levels [7]. Evidence from placebo-controlled clinical trials indicates that ERT can reduce or normalize plasma GL-3 levels [8–11] but no prospective studies have been carried out to date to determine a specific GL-3 threshold associated with improved outcomes.

The therapeutic goal for plasma GL-3 is to reduce levels as much as possible, ideally to (near-)normal values within 6 months. Failure to achieve (near-)normalization of plasma GL-3 levels may be an
indication for intensification of ERT and evaluation of anti-ERT immunoglobulin G (IgG) antibodies, although it remains unclear how GL-3 clearance affects prognosis.

3.2 Plasma lyso-GL-3

Plasma lyso-GL-3 is elevated in adult and paediatric male and female patients with Fabry disease [7,12–14], and may be a sensitive biomarker for monitoring response to ERT [7,15]. Lyso-GL-3 can be used as a biomarker to identify patients with classic and later-onset Fabry disease phenotypes, and as such may be more sensitive than plasma GL-3 as a marker of disease activity; however, lyso-GL-3 levels in females with the later-onset phenotype overlap with controls, which may be due to their heterozygosity and X-chromosome inactivation patterns [16].

The therapeutic goal for plasma lyso-GL-3 is to reduce lyso-GL-3 levels as much as possible. Failure to reduce plasma lyso-GL-3 levels to (near-)normal levels may be an indication to intensify ERT and evaluate anti-drug IgG antibodies [17]. No timeframe for monitoring the lyso-GL-3 response to ERT has been included at this time and needs further research.

3.3 Urinary GL-3

Based on the finding that the concentration of GL-3 in urine samples from male patients was significantly higher than in controls, measurement of urinary GL-3 (using mass spectrometry) was considered as a possible non-invasive screening method for Fabry disease [18]. More recent evidence has confirmed that urinary GL-3 levels are elevated in patients with Fabry disease [16,19]. Most female patients, with the exception of those with late-onset phenotype disease, usually have increased urinary GL-3 levels [7,20]; although some exceptions may be encountered [21], normal levels cannot exclude Fabry disease diagnosis, similarly to plasma (lyso)GL-3.

Urinary GL-3 levels may also be suitable for the diagnosis of Fabry nephropathy and monitoring the effect of ERT in patients with Fabry disease [22–24]. Further research is needed to explore the use of urinary GL-3 as an additional therapeutic goal for Fabry nephropathy and no goal has been included at this time.

3.4 Renal tissue GL-3

In Fabry disease, GL-3 accumulation occurs in several renal cell types, including podocytes, mesangial and interstitial cells, vascular endothelial and smooth muscle cells, as well as the tubular cells of the proximal and distal tubules and loop of Henle. The degree and pattern of accumulation of GL-3 in the kidney, as well as the extent of non-specific lesions of chronic damage can be evaluated histologically by kidney biopsy. Kidney histology can also identify important pathological processes
(such as foot process effacement) that are early markers of nephropathy occurring before overt clinical manifestations (such as albuminuria or abnormal estimated glomerular filtration rate [eGFR]) [25–29]. Performing repeated renal biopsy is low risk [30] and can help guide changes in drug dose and/or therapy if needed [31,32].

ERT has been shown to be very effective in clearing GL-3 deposits from a wide range of kidney cell types including vascular endothelium, glomerular mesangial cells, epithelial cells, interstitial cells of the cortex, and, to a lesser extent, from podocytes [31,33–35]. Clinical trials have reported clearance of GL-3 from endothelial cells within 6 months to 1 year of initiating treatment [8,9,34–36]. Furthermore, one study also revealed that 12 months’ treatment with agalsidase beta 1.0 mg/kg every other week (EOW) reduced GL-3 accumulation from podocytes in adult males [36]. An observational study has shown that clearance of GL-3 from podocytes is achievable in young patients but is dependent on the cumulative ERT dose. Patients receiving agalsidase 0.2 mg/kg EOW did not achieve GL-3 clearance from podocytes, whereas patients receiving agalsidase beta 1.0 mg/kg EOW) showed significant clearance [31]. Although the link between kidney GL-3 clearance and renal outcomes in adults has not been clearly established, the expert consensus was that renal endothelial cells deposits and possibly other renal cell types should be cleared in all patients to avoid progressive tissue damage and the GL-3 deposits from podocytes should be removed within 5 years.

4. Heart involvement

Cardiac manifestations are common in Fabry disease, occurring in 40–60% of patients [37–41]. The spectrum of cardiac complications is similar in both the classic and the later-onset cardiac phenotype and includes left ventricular hypertrophy (LVH), conduction abnormalities, bradycardia and chronotropic incompetence, supraventricular and ventricular tachyarrhythmias, myocardial fibrosis, valve disease, and microvascular dysfunction [42,43].

Cardiac complications are the leading cause of death in male and female patients with Fabry disease [44]. As there are no specific guidelines for the management of cardiac manifestations in Fabry disease, patients are considered in accordance with existing clinical practice guidelines (e.g. the European Society of Cardiology guidelines for diagnosis and management of hypertrophic cardiomyopathy [45]), recognising that some recommendations do not always apply to Fabry disease.
4. Cardiac morbidity and mortality

Fabry disease is associated with a high burden of cardiac morbidity associated with premature mortality [42–44,46]. Fabry patients suffer from cardiac complications, predominantly heart failure and fatal ventricular arrhythmias [39,42,43,47]. LVH and fibrosis – underlying many of the Fabry-related cardiac complications – are particularly detrimental for cardiac health and it is assumed that management of these conditions would have a major impact on morbidity and mortality [11,39,48–51]. Therapeutic goals for morbidity and mortality are therefore to reduce morbidity and avoid premature mortality in patients with early-stage cardiomyopathy, and to decrease morbidity and avoid premature mortality in patients with advanced cardiomyopathy (Table 1 [45,52–56]).

4.1 LVH

Cardiomyopathy in Fabry disease is characterised by LVH and an increase in left ventricular mass (LVM). Approximately one third of female and up to half of male patients will develop LVH-related cardiac symptoms [38].

A registry analysis revealed that LVH is present in 53% and 33% of untreated male and female patients, respectively, and increases with age [46]. The mean age of patients with LVH was 45 ± 9 years in untreated males and 54 ± 13 years in untreated females [46]. Clinical and observational evidence suggests that cases of mild and moderate LVH can be improved with ERT, whereas patients with severe LVH can be stabilized [11,48,57–62]. Clinical experience indicates that sustained treatment is required to determine the response of LVH to ERT [38,49,57].

The mechanisms of regression of LVH remain unclear, but are thought to involve clearance of cardiomyocyte GL-3 deposits and a reduction of trophic stimuli [50,60]. The optimal goal of treatment is to achieve normalization of LVH, but this is probably unachievable in most patients, particularly in those with myocardial fibrosis [60]. Therefore, a more realistic goal is to prevent progression of LVH on the unproven assumption that this translates into improved patient outcome. The consensus therapeutic goals for LVH are shown in Table 1.

Diagnosis of LVH is usually made initially by echocardiography to assess the extent and pattern of LVH and evaluation of cardiac dysfunction. The expert opinion of this panel is that magnetic resonance imaging (MRI) techniques with gadolinium late enhancement [56] and evaluation of tissue characteristics should also be used in monitoring patients, unless contraindicated by severe kidney impairment or the presence of an implanted cardiac device. Cardiac MRI offers higher definition of ventricular structures and visualization of the extent of scarring and fibrosis and more reproducible quantification of LVH for serial within-patient assessments [63]. It should be noted that in female patients, cardiac fibrosis may be present before LVH.
Table 1. Therapeutic cardiac goals for patients with Fabry disease.

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Therapeutic goals</th>
</tr>
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<tbody>
<tr>
<td>Cardiac morbidity and mortality</td>
<td></td>
</tr>
<tr>
<td>Early cardiomyopathy</td>
<td>• Avoid morbidity and premature mortality</td>
</tr>
<tr>
<td>Advanced cardiomyopathy</td>
<td>• Decrease morbidity and avoid premature mortality</td>
</tr>
<tr>
<td><strong>Left ventricular hypertrophy</strong></td>
<td></td>
</tr>
<tr>
<td>No LVH</td>
<td>• Prevent development of hypertrophy</td>
</tr>
<tr>
<td>Any LVH</td>
<td>• Prevent further progression and achieve stabilization of LVH, and prevent complications</td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td></td>
</tr>
<tr>
<td>No fibrosis(^a) (patients without detectable fibrosis)</td>
<td>• Prevent development of fibrosis</td>
</tr>
<tr>
<td>Mild(^a) (fibrosis in no more than 1 LV segment) or severe(^b) (≥2 fibrotic LV segments)</td>
<td>• Stabilize/prevent progression of fibrosis</td>
</tr>
<tr>
<td><strong>Arrhythmia (see ESC hypertrophic cardiomyopathy guidelines [45])</strong></td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>• Prevent sudden cardiac death by implantation of an implantable cardioverter defibrillator in patients with sustained ventricular arrhythmia or features suggestive of increased sudden death risk</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter(^b)</td>
<td>• Prevent stroke by oral anticoagulation with VKA in patients who develop persistent, permanent or paroxysmal AF or flutter</td>
</tr>
<tr>
<td></td>
<td>• Reduce heart failure symptoms by restoration of sinus rhythm or by controlling the ventricular rate</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>• Improve symptoms caused by chronotropic incompetence by improving heart rate response during effort</td>
</tr>
<tr>
<td></td>
<td>• Prevent sudden cardiac death, syncope or heart failure in patients with atrioventricular block with pacemaker implantation</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
</tr>
<tr>
<td>(see ESC heart failure guidelines [53])</td>
<td>• Improve exercise tolerance, normal daily activities, and QoL in patients with heart failure symptoms</td>
</tr>
<tr>
<td></td>
<td>• Prevent functional deterioration (as evidenced by an increase in the NYHA class)</td>
</tr>
<tr>
<td></td>
<td>• Prevent hospitalization or death due to heart failure</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reduce cardiovascular morbidity and mortality by optimal blood pressure control as described in the current guidelines for management of hypertension</td>
</tr>
</tbody>
</table>
4.3 Fibrosis

Myocardial fibrosis is a common feature in Fabry cardiomyopathy [39,50,55,60,62,64] and is a marker for poor prognosis [65,66]. Myocardial fibrosis in Fabry disease is associated with increased risk of malignant ventricular arrhythmias and sudden cardiac death [50]. Clinical evidence suggests that ERT does not prevent the development of fibrosis in patients with advanced Fabry cardiomyopathy [39,50]. In the absence of evidence showing regression of fibrosis, the consensus goals for fibrosis are to slow progression or prevent fibrosis.

4.4 Arrhythmia

Data on the prevalence and treatment of arrhythmia are mainly derived from registries, observational studies, and case reports [39,43,46,67]. In the FOS, among 336 ERT-treated patients the prevalence of arrhythmia was 33% and 38% for male and female patients, respectively [46]. In a prospective observational study of 207 patients with Fabry disease (including treated and untreated patients) followed for 7 years, 6% developed atrial fibrillation, and 6% received devices (i.e. a pacemaker or internal cardioverter defibrillator) for the treatment of bradycardia [43]. The high incidence of pacemaker implantation, atrial fibrillation, and ventricular arrhythmias indicates that arrhythmia has a significant impact on the natural history of the disease [43]. Antiarrhythmic treatment with amiodarone is not recommended because of a reported interference with ERT, though no clinical data is currently available to support this statement [63].

Patients have an increased incidence of non-sustained ventricular tachycardia; however, it is unclear whether or not there is an association between non-sustained ventricular tachycardia and sudden cardiac death. Clinical experience in the Fabry population indicates that sudden arrhythmic deaths are uncommon [43], but should be considered a risk in patients with ventricular arrhythmias and advanced stages of Fabry cardiomyopathy. Accordingly, in advanced stages of cardiomyopathy, loop recorders might be considered to detect arrhythmia [68].
There is no published evidence to suggest that ERT prevents cardiac arrhythmia of any kind. For this reason, the therapeutic goals for arrhythmia reflect conventional treatment guidelines for any cardiac disease. Regular monitoring of heart rhythm is key to the prevention of arrhythmia-related events such as stroke, heart failure and sudden cardiac death.

4.5 Heart failure

According to data from the Fabry Registry, heart failure occurs in 3.5% in men and 2.3% in women with Fabry disease [42]. A large longitudinal study reported severe heart failure (New York Heart Association [NYHA] ≥3) in 10% of patients [43]. Heart failure is related to age and disease progression. The NYHA classification can be used as a measure of the severity of heart failure and is predictive of Fabry disease progression [50]. Biomarkers such as high-sensitivity troponin and brain natriuretic peptide are also emerging as useful tools for assessing the extent and progression of Fabry cardiomyopathy/heart failure [69,70].

Symptoms of heart failure should be managed according to conventional heart failure guidelines, although there is no evidence for a prognostic benefit of standard therapies in patients with Fabry disease [63]. Clinical evidence for the management of heart failure in Fabry disease is mainly derived from observational studies [60,71]. One study showed improvements in NYHA classifications in patients who were treated with ERT for 10 years [71]. Indirect evidence for improved heart failure is provided by another study that reported improved strain and exercise capacity in patients who did not have fibrosis and were treated with ERT for 3 years [60]. Therapeutic goals for heart failure in Fabry disease are therefore to improve exercise tolerance and normal daily activities, as well as to improve or prevent progression of NYHA classification (Table 1).

4.6 Cardiovascular risk factors

Fabry patients may have one or more general risk factors for cardiovascular disease (e.g. systemic hypertension, hypercholesterolaemia, diabetes, smoking) as well as those resulting from the Fabry disease process (e.g. decreased glomerular filtration rate [GFR], pathological albuminuria, cardiomyopathy), and its treatment (e.g. carbamazepine or tricyclic antidepressants). Clinically silent or minor cardiovascular manifestations are very common in Fabry patients of both genders [46] and can progress over time to major cardiovascular events (heart failure, stroke, and sudden cardiac death) [42]. Data from the Fabry Registry showed that, prior to starting ERT, 5.8% of men and 3.7% of women experienced cardiovascular events at mean ages of 45 and 54 years, respectively [42]. Hypertension and LVH were identified as risk factors that most strongly associated with the
occurrence of cardiovascular events [42], although Fabry disease may itself be considered a major risk factor for cardiovascular events.

An observational study of 5-year follow-up data from 362 patients in the Canadian Fabry Disease Initiative indicated that modification of cardiovascular risk factors with adjunctive therapies together with ERT reduced the risk of adverse outcomes related to the disease [72]. Use of adjunctive therapies such as aspirin (78%), renin-angiotensin blockade (59%), and statins (55%) was high in this cohort of ERT-treated patients with Fabry disease [72]. Other publications have also indicated that treatment of Fabry disease with ERT and statins reduces the risk of cardiovascular events [11,49,73,74].

Increased systemic blood pressure is a significant risk factor for heart failure, and blood pressure control has been used as an objective measure of heart failure in non-Fabry disease populations [75,76]. While the prevalence of systemic hypertension in patients with Fabry disease may not differ from the general population, elevated systemic blood pressure has been shown to negatively impact the progression of Fabry cardiomyopathy [55] and a common goal for blood pressure control has been included in this set of treatment goals. It must be stated that antihypertensive treatment must be individualized for each patient in order to avoid hypotension (Table 1).

Neither primary nor secondary prevention of established cardiovascular risk factors have been systematically studied in the Fabry patient population but consideration should be made for Fabry disease-specific contraindications with general cardiovascular treatments (such as avoiding hypotension when using blood pressure lowering agents in patients treated with antiproteinuric drugs for Fabry nephropathy). Overall, the therapeutic goal is to apply prevention of cardiovascular risk factors according to established guidelines (Table 1).

5. Kidney involvement

The cellular kidney pathology is associated with progressive CKD with increasing albuminuria leading to overt proteinuria and reduced GFR, ultimately progressing to end-stage kidney disease (ESKD), if untreated [77]. Microscopic haematuria and nephrotic proteinuria are relatively uncommon manifestations of Fabry nephropathy. The renal complications of Fabry disease are key contributors to the morbidity and mortality associated with the disorder [78]. Effective management of underlying kidney pathology hinges upon early diagnosis and timely initiation of ERT at a young age [31]. Registry and clinical trial data have shown that patients who initiate ERT at a younger age, soon after the onset of symptoms, benefit the most from ERT and have more favourable long-term renal outcomes [11,77,79,80]. This is because significant glomerular and vascular damage can
develop prior to the emergence of albuminuria or changes in GFR, and seems reversible only at an early stage in the pathogenetic process [25,26,77,79].

Additional treatment with non-specific therapies such as angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) as needed for the control of proteinuria and high blood pressure may be beneficial in stabilizing kidney function or slowing its decline [27,80,81].

The overall therapeutic goals for Fabry nephropathy, depending on the individual patient’s clinical condition, are to prevent the development of albuminuria, stabilize albuminuria or prevent, avoid, or delay progression to overt proteinuria, and stabilize kidney function. The degree of albuminuria/proteinuria and the GFR level can be readily monitored clinically and provide useful non-invasive markers of severity in Fabry nephropathy and of response to therapy.

5.1 Glomerular filtration rate (GFR)

GFR is an established indicator of CKD and CKD progression, and is used as a marker of kidney function and therapeutic efficacy in Fabry disease [78,79]. Although measured GFR is considered the gold standard method for evaluating renal function, it is not performed routinely in all centres. Estimated GFR (eGFR) is more regularly used to assess renal function in patients with Fabry disease. The Chronic Kidney Disease Epidemiology Collaboration equation should be used to calculate eGFR in all adult patients [82]. For GFR assessment in children, the updated Schwartz formula [83] is recommended [84].

In the context of managing renal function in Fabry nephropathy, patient-specific natural history data are used to estimate the annual loss of eGFR. It should be noted that CKD progression is faster in Fabry patients with more advanced CKD [85]. Stabilization of function is achieved if a patient has a GFR slope loss ≤1–3 mL/min/1.73m²/year [86], as a loss of up to 1 ml/min/1.73m²/year is considered normal for individuals over the age of 40 years. This can be attained in patients with early stage CKD and little proteinuria who are treated soon after emergence of symptoms, but patients with more advanced disease often show continued decline in GFR [77]. Progression of renal disease is demonstrated by an annual decrease in GFR >3 ml/min/1.73m² and is considered fast when the rate of progression is > 5 mL/min/1.73m² [84,87]. A response to treatment will reduce the annual slope loss to <3 ml/min/1.73m². For patients with fast renal progression, slowing the process to <5 ml/min/1.73m²/year, or more than 50% decrease in progression is also clinically valuable. It should be noted that some patients do not fully achieve the eGFR therapeutic goal because of a more advanced level of tissue damage when ERT is initiated. Patients with similar baseline CKD stage
and level of albuminuria, for example, may respond differently to optimal therapy, depending on the extent of kidney tissue damage present prior to treatment [11].

The overall therapeutic goal for management of eGFR (at any stage of disease) is to stabilize or reduce the slope loss of eGFR, and avoid or delay progression of CKD to ESKD and the need for renal replacement therapy. For paediatric patients with normal eGFR when initiating ERT, the therapeutic goal should be to keep renal function normal (Table 2).

Renal replacement therapies include dialysis and kidney transplantation, which is the optimal renal replacement therapy for patients with Fabry disease and ESKD [88].

Table 2. Therapeutic renal goals for patients with Fabry disease.

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Therapeutic goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td></td>
</tr>
<tr>
<td>No kidney involvement&lt;sup&gt;a&lt;/sup&gt;</td>
<td>eGFR should be maintained in an age-appropriate normal range&lt;sup&gt;a&lt;/sup&gt; [87]. Avoid eGFR loss</td>
</tr>
<tr>
<td>Mild kidney involvement, eGFR at normal levels&lt;sup&gt;b&lt;/sup&gt; or hyperfiltration (eGFR &gt;90 ml/min/1.73m²)</td>
<td>eGFR should be maintained in an age-appropriate normal range&lt;sup&gt;b&lt;/sup&gt; [87].</td>
</tr>
<tr>
<td>Mild-to-moderate kidney function impairment, mild eGFR decreases (eGFR 60–90 ml/min/1.73m²)</td>
<td>Prevent progression of eGFR loss and stabilize eGFR level</td>
</tr>
<tr>
<td>Moderate-to-severe kidney function impairment, mild-to-moderate eGFR decreases (eGFR 45–59 ml/min/1.73m²)</td>
<td>Prevent progression of eGFR loss to delay/avoid ESKD</td>
</tr>
<tr>
<td>Moderate-to-severe eGFR decreases (eGFR 30–44 ml/min/1.73m²)</td>
<td>Prevent progression of eGFR loss to delay/avoid ESKD</td>
</tr>
<tr>
<td>Severe eGFR decreases (eGFR 15–29 ml/min/1.73m²)</td>
<td>Decrease the slope of eGFR as much as possible; delay the progression to ESKD</td>
</tr>
<tr>
<td>ESKD</td>
<td>Provide optimal renal replacement therapy by dialysis or kidney transplantation, maintain ERT to avoid damage to heart and CNS. Suggest and encourage kidney transplantation before dialysis (from a living donor when possible) to prevent impact on other organs</td>
</tr>
<tr>
<td>Albuminuria (mg/g)</td>
<td></td>
</tr>
<tr>
<td>General: all patients</td>
<td>Keep albuminuria levels as low as possible</td>
</tr>
<tr>
<td>Mild-to-moderate kidney function impairment; albuminuria levels:</td>
<td>Normalize/stabilize albuminuria</td>
</tr>
<tr>
<td>&lt;30 mg/g (&lt;3 mg/mmol)</td>
<td>Albuminuria levels: 30–300 mg/g (3–30 mg/mmol)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• Normalize/stabilize albuminuria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albuminuria levels: &gt;300 mg/g (&gt;30 mg/mmol)</th>
<th>Moderate-to-severe kidney function impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Reduce levels to &lt;300 mg/g (30 mg/mmol)</td>
<td>• Slow progression of albuminuria</td>
</tr>
</tbody>
</table>

CNS, central nervous system; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; * A normal level usually refers to eGFR 90–120 ml/min/1.73m² [87].

5.2 Albuminuria and proteinuria

Albuminuria and proteinuria are independent diagnostic criteria for CKD irrespective of its cause, and strong independent risk factors for CKD progression in male and female Fabry patients [27,77,89]. Therapies that decrease albuminuria or proteinuria have been shown to reduce the risk of CKD progression [27,80,89]. In Fabry nephropathy, there is a relationship between CKD stage and degree of proteinuria; higher degrees of proteinuria are usually seen in patients with more advanced CKD, and higher baseline proteinuria levels have also been shown to be a significant indicator of faster GFR decline [11,86].

In general, the therapeutic goal for albuminuric/proteinuric patients with Fabry disease should be to reduce albuminuria/proteinuria levels (Table 2). This requires the use of adjunctive therapies (e.g. ACEi or ARB) in addition to ERT, as ERT alone does not appear to have significant effects on proteinuria, though there is evidence that ERT can reduce (micro)albuminuria [31,77,86,90]. Additionally, it is important to initiate ERT early in the disease course as substantial, irreversible organ damage can occur prior to overt proteinuria [49,77,91,92]. For paediatric and adult patients with normal urinary albumin excretion levels when initiating ERT, the therapeutic goal should be to avoid the development of albuminuria (Table 2).

6. Brain and peripheral nervous system involvement

The first neurological symptoms of Fabry disease occur in the peripheral nervous system (PNS) as a result of damage to neurons. Small, unmyelinated or thinly myelinated nerve fibres are particularly affected and small fibre peripheral neuropathy contributes to peripheral neuropathic pain (chronic and acute excruciating pain), and accounts for dysesthesias, deficits of thermal sensation and of physiologic pain perception, neuropathic pain, impaired sweating, GI dysmotility, and other sensory deficits (e.g. hearing loss) [93–97]. The relation between small nerve fibre
function, age, disease severity, and pain in Fabry disease is difficult to elucidate, but increasing age and disease severity can be associated with a reduction in pain, although patients may then develop symptoms related to large nerve fibre impairment [94,96]. In the central nervous system (CNS), chronic white-matter hyperintensities develop, and cerebral vasculopathy leads to an increased risk of acute ischaemic cerebrovascular events [98]. Neuropsychological dysfunction can occur and depression (often associated with chronic pain) is common among patients [99,100].

Some neurological symptoms/signs (e.g. GI symptoms and pain) of Fabry disease are present in both children and young adults, whereas others (e.g. cerebrovascular disease manifestations) tend to develop later in life. ERT and other adjunctive therapies (pain management, stroke prophylaxis) are useful. While ERT cannot cross the blood–brain barrier, early ERT initiation might slow or stop cerebrovascular disease and thus prevent stroke occurrence.

6.1 Neuropathic pain due to small fibre neuropathy

Fabry-related neuropathic pain is one of the earliest clinical symptoms reported by patients; it is experienced by 60–80% of classically affected boys and girls, usually occurring at an earlier age in boys than in girls [101,102]. A study that evaluated the types and characteristics of pain experienced by Fabry patients [103] classified Fabry pain into four main types: evoked pain (allodynia or hyperalgesia), pain attacks, permanent (chronic) pain, and pain crises. Pain crises consist of episodes of extreme pain usually originating in the extremities and spreading over the body, lasting from hours to days and often resistant to analgesic treatments [103]. Patients may experience one or more of these types of Fabry-related pain, the pattern of which may change over time.

One of the factors behind Fabry pain development is a progressive, length-dependent reduction in the density of small thinly myelinated Aδ nerve fibres and the unmyelinated C fibres in the peripheral somatic and autonomic nervous systems, and functional impairment of small nerve fibre conduction [93,94,96,101,104]. Damage of small nociceptive neurons causes functional changes in signal generation, i.e. spontaneous activity in these neurons, and secondary sensitization of nociceptive neurons in the central nervous system. Furthermore, descending modulatory pathways are altered in neuropathic pain leading to further sensitization [91].

Fabry patients also exhibit dysfunctions in somatosensory processing thought to be involved in pain generation, such as deficits in discrimination of cold stimuli. Besides these nerve-dependent mechanisms of pain generation, an alternative still hypothetical concept assumes that sensory abnormalities and pain might be due to blood flow changes in neuronal and other peripheral tissues; the vasa nervorum, which supply peripheral nerves, may be affected. Theoretically, altered
microcirculation due to GL-3 accumulation might induce consecutive peripheral nerve dysfunction and nociceptor activation [105].

While the perception of pain is subjective, its assessment should be objective and conducted carefully. Appropriate, regular assessment of pain levels/impact allows monitoring of the progression of pain and efficacy of treatment. There is substantial variation in the tools used to assess pain in Fabry disease. General pain assessment tools can be used, such as the McGill Pain Questionnaire, the Brief Pain Inventory (BPI) [94], or the Total Symptom Score [106] but there are also several Fabry-specific pain questionnaires that can be useful such as the Würzburg Fabry Pain Questionnaire for adults [107], Fabry-specific Paediatric Health and Pain Questionnaire [108], and the FabryScan questionnaire [109]. Expert consensus of this panel was that the Würzburg Fabry Pain Questionnaire, developed in adult patients, is the preferred tool to assess pain in Fabry disease [107,110].

Patients require an individual pain-management strategy, which should include advice on lifestyle modifications (e.g. use of air conditioning to avoid overheating, the importance of good hydration) that can help to avoid pain triggers/pain crises. The experience of some experts indicates that ERT can be effective in the management of neuropathic pain. Some studies [111-115] suggest a benefit of ERT on pain, however, other studies report no, or a limited, effect of ERT on pain [10,21,103]. This expert consensus panel suggests that ERT could be considered at the onset of pain to limit peripheral nervous system damage, although further evidence is needed to support this recommendation. To manage the neuropathic pain symptoms, adjunctive pharmacotherapy should follow recommendations for neuropathic pain states of other aetiologies [116,117]. Many patients still suffer from neuropathic pain despite ERT and therefore intensified adjunctive pain management should be considered. Exercising clinical caution in the selection of analgesics for symptomatic treatment of neuropathic pain is important to avoid undesirable side effects and potential addiction risks [94,118]. Based on currently available clinical evidence, tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors (e.g. duloxetine), carbamazepine, gabapentin, and pregabalin are suggested pain-management agents in Fabry disease, although treatment outcomes from several clinical trials are modest, and tricyclic antidepressant use may increase the risk of cardiac arrhythmia [118]. Lidocaine patches, high-strength capsaicin patches, and tramadol are second-line options, while strong opioids (preferably controlled-release formulations) should be reserved as a last resort third line of treatment, considering the reported chronic opioid abuse epidemic [119]. Caution should be paid to waning of pain at adult age in absence of ERT and symptomatic treatment as this may represent neuropathy progression rather than stabilization of Fabry disease. Additionally, as the manifestations of Fabry-related neuropathic pain vary widely from patient to patient and individual
patients have different patterns of sensory abnormalities, future research is required to determine whether there are specific subgroups of patients with Fabry disease with distinct neurological phenotypes that might benefit from a stratified approach to pain management. Such an approach has been recognized as an important area for future pain management strategies in other pain disorders [91].

While the optimal therapeutic goal is to eliminate pain, a more realistic goal is to reduce pain to manageable levels, avoid pain progression, and reduce the number of pain crises (Table 3). Despite differences in the timing of onset of pain, the same therapeutic goals apply to both genders.

Table 3. Therapeutic goals for neuropathic pain in patients with Fabry disease.

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Therapeutic goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathic pain due to small fibre involvement</strong></td>
<td></td>
</tr>
<tr>
<td>Early-stage disease</td>
<td>• Reduce the intensity of pain and/or frequency of pain crises</td>
</tr>
<tr>
<td>Late-stage disease</td>
<td>• Reduce pain to manageable levels</td>
</tr>
<tr>
<td>Paediatric patients</td>
<td>• Alleviate pain generally, and reduce the number of pain crises</td>
</tr>
<tr>
<td><strong>Pain due to entrapment neuropathy</strong></td>
<td></td>
</tr>
<tr>
<td>General: all patients</td>
<td>• Try to reduce pain as much as possible</td>
</tr>
<tr>
<td></td>
<td>• Attempt to avoid lesions, and be aware of and manage pain due to nerve compression/entrapment (e.g. carpal tunnel syndrome)</td>
</tr>
</tbody>
</table>

6.2 Neuropathic pain due to entrapment neuropathy

Neuropathic pain associated with entrapment neuropathy can have a negative effect on patients’ QoL in late-stage Fabry disease. While not specific to Fabry disease, carpal tunnel syndrome due to nerve compression is common in Fabry disease, occurring in up to 25% of patients; its symptoms should not be mistakenly diagnosed as Fabry disease-related neuropathy [120]. Carpal tunnel syndrome can be managed with standard care and surgical decompression surgery [120]. Therapeutic goals for the management of pain due to entrapment neuropathy include maximal pain reduction and targeted pain management to reduce nerve compression or entrapment (e.g. in carpal tunnel syndrome (Table 3).
6.3 Cerebrovascular manifestations

Cerebrovascular manifestations of Fabry disease include clinical manifestations (transient ischaemic attacks [TIAs] and strokes) and neuroradiological findings (chronic white matter hyperintensities and the basilar artery dolichoectasia) [98]. All these features usually occur at an earlier age than is seen in the general population. Evidence from registry studies has shown that in patients with Fabry disease the incidence of stroke is markedly higher than in the general population across all age groups and in both males and females [121]. GL-3 accumulation in the endothelium of intracranial blood vessels leads to vasculopathy, which can increase the risk of TIA and ischaemic stroke [121]. Other factors also play a role in the pathology of cerebrovascular Fabry complications, like increased hyperhomocysteinaemia [122], factor V of Leiden, and other prothrombotic factors [98], plasma levels of pathogenic lysoGL-3 [13] and arrhythmia-triggered embolism. The assessment of concomitant prothrombotic factors and the monitoring of changes in cerebral blood flow velocities with Doppler sonography are relevant to determine the increased risk of stroke for patients with Fabry disease. A description of the pathological processes underlying the cerebrovascular manifestations of Fabry disease is outside the scope of this paper, but has recently been reviewed concisely [98].

In a Fabry Registry study of 2,446 patients, 7–32% of females and 11–48% of males experienced strokes, and the patients who experienced strokes were more likely to have also experienced a TIA [121]. The majority of strokes were ischaemic (86.8% of 132 patients experiencing stroke), although haemorrhagic strokes also occurred in 16.9% of males and 6.9% of female patients [121].

Registry data and a recent review of cohort studies suggest a beneficial effect of ERT on the incidence of a composite clinical outcome which includes cardiovascular and cerebrovascular events including stroke [49,123]. However, data are not available showing a beneficial effect of ERT on TIA/stroke as an isolated endpoint at this time. While the expert panel felt that it may be possible to reduce the risk of TIA/stroke in patients with Fabry disease or delay the onset of such complications by starting treatment at an early age using ERT in combination with antithrombotic drugs, currently, there are not enough data to support this recommendation. Prevention of TIA/stroke later in the disease process is not possible because of pre-existing irreversible damage to the cerebral vasculature, although a reduction in the rate of stroke recurrence may be possible. To this end, general primary and secondary stroke prevention measures should be strictly followed for all patients [124,125]. The formation of chronic white matter hyperintensities in the CNS creates the potential risk for stroke, cognitive decline, dementia, and death in male and female patients [126].

White matter hyperintensities are non-specific, age-related, frequently detected among those over 50-60 years in the general population, but can appear earlier in Fabry disease due to...
progressive microvascular involvement. In one study, 63% of Fabry disease patients were reported to have white matter hyperintensities [126], although another publication noted that nothing about the presence or extent of white matter hyperintensities could distinguish between patients with Fabry disease versus those with non-Fabry related cerebrovascular events [127]. The 4th decade of life seems to be critical for the progression of white matter hyperintensities [128], but there seems to be no strong correlations between white matter hyperintensities and other typical Fabry disease phenotype manifestations such as renal or cardiac involvement, pain scores, enzyme activity or lyso-GL-3 levels [126,128]. Although there have been no studies on the effect of ERT on early-stage disease, a placebo-controlled phase 4 study in 41 patients has suggested that the progression of white matter hyperintensity burden may be delayed with ERT [126].

The prevalence of vertebrobasilar dolichoectasia among the Fabry disease population is not well defined, but recent data showed that it could be an early marker of cerebrovascular disease [129]. Basilar artery dolichoectasia in Fabry disease is due to extensive remodelling of the vessel. The morphological changes are regarding the diameter, the elongation, and the tortuosity of the basilar artery. These features differ according to age and gender of the patients [130]. The effect of long-term ERT on basilar artery diameter has not yet been specifically addressed [98].

In general, the therapeutic goals for cerebrovascular manifestations of early-stage Fabry disease should be to reduce the risk and avoid the occurrence of TIA or stroke. At later stages, the goal should be to prevent recurrence of TIA or stroke (Table 4).

Table 4. Therapeutic goals for cerebrovascular manifestations in patients with Fabry disease.

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Therapeutic goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIA/stroke</strong></td>
<td></td>
</tr>
<tr>
<td>Patients without events</td>
<td>• Prevent occurrence of TIA/stroke and delay age at onset of first event</td>
</tr>
<tr>
<td>Patients with ≥1 event</td>
<td>• Prevent recurrence of TIA/stroke</td>
</tr>
<tr>
<td><strong>Chronic white-matter hyperintensities</strong></td>
<td></td>
</tr>
<tr>
<td>Early-stage disease</td>
<td>• Prevent development of hyperintensities</td>
</tr>
<tr>
<td>Late-stage disease</td>
<td>• Delay progression of number and volume of hyperintensities</td>
</tr>
</tbody>
</table>

TIA, transient ischaemic attack.
6.4 Neuropsychological dysfunction

Currently available clinical evidence indicates that cognitive impairment can be present in Fabry disease and includes impaired information processing and reduced executive function performance (e.g. verbal generation, reasoning, problem solving), particularly in males [99,131–133]. Patients who manifest cognitive impairment are also more likely to report symptoms of anxiety and depression [99]. Depression is an under-recognized problem in Fabry disease; it develops in nearly 50% of patients, with a slightly higher prevalence in males than females, and more than 25% of patients experience severe depression [134]. As patients often experience chronic neuropathic pain and there is a strong association of chronic pain with depression, it is also important to manage Fabry-related pain adequately, with regular assessment and use of appropriate pharmacological therapies [95,117,118].

Psychiatric and neuropsychological evaluations have been recommended as part of the assessment of patients with Fabry disease [131]. The therapeutic goals for neuropsychological dysfunction include the prevention of progression of cognitive impairment and adequate monitoring and control of symptoms of depression and anxiety.

6.5 Other manifestations of Fabry disease related to neurological pathology

6.5.1 Hearing loss and vertigo

Fabry disease-associated hearing loss can be progressive or sudden [135], and can arise for different reasons. Symptomatic hearing loss has been reported in 18–55% of patients, sudden hearing loss in 6–36%, and tinnitus in 17–53%. Phenotype differences have been shown to be significantly different at ultra-high frequencies, with classic patients showing more hearing loss than late-onset patients of both genders [136]. Hearing impairment can involve the cochlea, retrocochlea, acoustic vessel supply, or brainstem, thus hearing loss may be attributed to the PNS or CNS (i.e. sudden hearing loss) [137]. It is important to know the cause of hearing impairment prior to treatment initiation; audiometry testing and neurological investigations should therefore be carried out at diagnosis and at regular intervals following diagnosis. Clinical evidence indicates that progressive hearing loss can be stabilized, but not reversed, by ERT treatment [136]. Expert experience indicates that the frequency of sudden hearing loss decreases during ERT compared with the frequencies observed in untreated patients [135]. Sudden hearing loss cannot be reversed by ERT even when treatment is initiated early, though studies examining sudden hearing loss prevention with ERT have yet to be performed.
Vertigo and tinnitus aurium are other symptoms often reported by patients [1,135]. In one study of 20 patients with Fabry disease, 30% reported symptoms of vertigo [138]. However, it is currently unclear whether vertigo and tinnitus can be improved with ERT.

Therapeutic goals for hearing loss include stabilization of hearing loss, the possible use of hearing aids or cochlear implants [139] to improve both hearing and patient QoL [1], and managing patient expectations about the likelihood of hearing restoration (Table 5 [140–142]).

Table 5. Therapeutic goals for other manifestations of Fabry disease related to neurological pathology.

<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Therapeutic goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td></td>
</tr>
<tr>
<td>Progressive hearing loss</td>
<td>• Stabilize hearing; appropriately address hearing loss with suitable devices to avoid education/occupational/social impacts</td>
</tr>
<tr>
<td>Sudden hearing loss</td>
<td>• Manage patient expectations about the use of treatment and likelihood of restoration of hearing</td>
</tr>
<tr>
<td>Gastrointestinal dysfunction</td>
<td></td>
</tr>
<tr>
<td>General goal</td>
<td>• Mitigation of GI symptoms to improve QoL</td>
</tr>
<tr>
<td></td>
<td>• Monitor GI symptoms using validated GI rating scales</td>
</tr>
<tr>
<td></td>
<td>(Rome III or the GSRS [140,141], the Bristol stool form scale [142])</td>
</tr>
<tr>
<td>Early-stage disease</td>
<td>• Avoid or reduce GI symptoms</td>
</tr>
<tr>
<td>Late-stage disease</td>
<td>• Prevent progression of GI symptoms</td>
</tr>
<tr>
<td>Hypohidrosis</td>
<td></td>
</tr>
<tr>
<td>General goal</td>
<td>• Increase sweating and decrease the episodes of unexpected fever</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; GSRS, Gastrointestinal Symptom Rating Scale; QoL, quality of life.

6.5.2 Gastrointestinal dysfunction

GI symptoms are some of the earliest and most commonly reported symptoms in Fabry disease, and include abdominal pain, bloating, diarrhoea, constipation, nausea, and vomiting [101,140,143,144]. One study found that GI symptoms occurred in approximately 60% of children and in 50% of adults, and had a serious negative effect on QoL [143]. However, these numbers may not reflect the true occurrence of GI symptoms in patients with Fabry disease, specifically. One major limitation of this study was that it lacked a control group of patients who did not have Fabry disease: GI symptoms are often also highly prevalent in the general population, and may also vary.
significantly per geographical region or patient population [145–148]. Pathophysiology of GI
dysfunction in Fabry disease includes intestinal dysmotility and impaired autonomic function,
vasculopathy, and myopathy in the gut. Malabsorption of nutrients due to glycosphingolipid deposits
affecting the intestinal villi can lead to failure to gain weight [149].

GI symptoms should be measured using a validated GI rating scale (e.g. Rome III or the
Gastrointestinal Symptom Rating Scale [GSRS]) [140,141] and the Bristol stool form scale [142];
these are sensitive measures of GI dysfunction and enable the progression of GI symptoms to be
monitored. Other techniques such as endoscopy, scintigraphy, video capsule endoscopy, and
intestinal biopsy can also be used to investigate GI symptoms [149,150].

Clinical evidence is available that ERT mitigates GI symptoms, in children and in adult male
and female patients [112,143,151–154]. Clinical experience further indicates that advising patients
to eat small frequent meals may help to alleviate GI symptoms. Therapeutic goals for GI dysfunction include the mitigation, reduction, and prevention of
progression of GI symptoms (Table 5).

6.5.3 Hypohidrosis

In addition to the clogging of sweat glands by glycosphingolipids, the small fibre neuropathy
associated with Fabry disease not only causes impaired sensitivity to heat and cold but also
contributes to hypohidrosis due to a dysfunction of sympathetic sudomotor fibres [93,95,155,156]
with consequences for hyperthermia, poor exercise tolerance, and altered fever manifestation.
Hypohidrosis has been reported to occur in 53% of males and 28% of females with Fabry disease
[157,158]. Peripheral sweat production can be measured with quantitative sudomotor axon reflex
tests; the sympathetic skin response is considered a less reliable test [159].

Clinical evidence indicates that ERT can improve sweat function and improves the ability to
perceive thermal stimuli, such as heat or cold [106,111,160]. Early ERT initiation is important to
minimize damage to the nerve fibres and preserve small nerve fibre function including heat and cold
sensation or sweating. The therapeutic goal for hypohidrosis is to normalize sweat function and
decrease the episodes of unexpected fever (Table 5).

7. Other manifestations of Fabry disease
7.1 Dermatological abnormalities/angiokeratoma

Dermatological abnormalities have been reported to be present in 78% of males and 50% of
females with the classic phenotype of Fabry disease [157]. Angiokeratoma is the most common
dermatological abnormality occurring in 66% males and in 36% females, and is the most visible early
clinical feature of classic Fabry disease. They typically appear as either single or groups of superficial small reddish purple skin lesions that increase in number and size with age [157,161]. Lesions appear on the umbilicus, hands, knees, elbows, and trunk spreading to the genitals during adolescence [161]. However, angiokeratomas of Fabry disease should not be confused with senile (“cherry”) angiomas [162].

Clinical experience suggests that the resolution of angiokeratomas via disease-specific ERT is unrealistic. The treatment goal, therefore, is to use nonspecific treatment options such as laser therapy to remove lesions [163] (Table 6).

Table 6. Therapeutic goals for other manifestations of Fabry disease.

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Therapeutic goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological abnormalities</td>
<td>• Remove lesions with nonspecific therapy</td>
</tr>
<tr>
<td>Ophthalmological manifestations</td>
<td>• Manage dry eye symptoms in patients with symptomatic conjunctival lymphangiectasia with usual treatments*</td>
</tr>
<tr>
<td>Bone manifestations</td>
<td>• Maintain normal or near-normal bone mineral density through adoption of osteopenia/osteoporosis prevention measures</td>
</tr>
<tr>
<td>Pulmonary manifestations</td>
<td>• Stabilize or improve lung function</td>
</tr>
</tbody>
</table>

* Monitoring cornea verticillata and fundus vessels regularly (every 5 years) is advised

7.2 Ophthalmological manifestations

Ophthalmological manifestations in Fabry disease include cornea verticillata, vessel tortuosity, Fabry cataracts [164] and symptomatic conjunctival lymphangiectasia [165]. Cornea verticillata does not impair vision, and can only be diagnosed through the use of slit-lamp eye examination. Up to 30% of patients with later-onset Fabry disease may present with corneal deposits, but the observation of typical cornea verticillata is highly predictive for the diagnosis of classic Fabry disease [1,166]. Registry data have shown that cornea verticillata is the most common ophthalmological manifestation; cornea verticillata was observed in more than 70% of males and females in a survey of 173 patients FOS who underwent ophthalmological examination [167]. Clinical evidence is limited but data from a retrospective observational study suggest that ERT may stabilize cornea verticillata in some patients with Fabry disease [168]. Fabry cataracts are posterior capsular cataracts with visible whitish spoke-like deposits of granular material [164,167]. Symptomatic
conjunctival lymphangiectasia seems relatively common in patients with classic Fabry disease; it causes dry eye symptoms and should be monitored frequently.

In terms of therapeutic goals for ophthalmological manifestations, the dry eye symptoms associated with symptomatic conjunctival lymphangiectasia can be managed with usual treatments for dry eyes and cornea verticillata should be monitored regularly (every 5 years) (expert opinion) (Table 6).

7.3 Bone manifestations

Bone manifestations of Fabry disease including osteopenia and osteoporosis, are characterized by low bone mineral density and deterioration of the bone structure that can lead to fractures [169–171]. These conditions may develop early in the disease and become severe. Several observational studies have reported that 50–87% of untreated Fabry patients have either osteopenia or osteoporosis [1,169–171]. In particular, one study of 44 patients, 18 of whom were treated with ERT, reported that low bone mineral density was highly prevalent in male patients at the femoral neck, and the male patients in this study demonstrated an increased incidence of non-traumatic fractures relative to the general population [171]. Patients with Fabry disease often have several factors which increase the risk of osteopenia or reduced bone mineral density, including use of anti-epileptic medications for pain [170,171], body weight and renal function impairment [169,170]. Clinical experience indicates that ERT does not have an effect on bone mineral density; therefore, patients should follow current recommendations regarding identification and treatment of vitamin D deficiency [172] and osteoporosis. The therapeutic goal for bone manifestations is to maintain normal or near-normal bone mineral density through adoption of osteopenia/osteoporosis prevention measures (Table 6).

7.4 Pulmonary manifestations

Male and female patients with Fabry disease can develop pulmonary manifestations, usually presenting as shortness of breath during exercise, chronic cough, and wheezing, with many patients having obstructive airway limitation [173,174]. It is not clear how much pulmonary involvement may contribute to cause dyspnoea in patients with Fabry disease, as asthma and chronic obstructive pulmonary disease are also prevalent in the general population [174]. On the other hand, although evidence on the effect of ERT on pulmonary involvement is limited, several case reports and an observational study suggest that symptoms can be improved or at least stabilized by treatment [175–177]. The impact of ERT may depend on the extent of lung involvement prior to treatment, as with other organ dysfunction in Fabry disease, and early initiation of ERT should be considered [174].
In general, the therapeutic goal for pulmonary manifestations is to stabilize or improve lung function (Table 6).

8. QoL in Fabry disease

Systematic review of clinical evidence has confirmed that patients with Fabry disease have a lower QoL compared with the general population [178]. Factors that reduce QoL in Fabry disease include Fabry-related chronic pain and pain crises, GI symptoms, hearing loss, physical inactivity, and fatigue. Importantly, the burden of organ damage also severely affects QoL. Experts note, however, that a diagnosis of Fabry disease followed by a treatment plan may improve QoL in some patients because of the psychological benefits of having a care team in place and monitoring their health.

A variety of general tools are available to assess QoL in Fabry patient populations, with the Short Form Health Survey (SF-36), the EuroQoL 5 Dimensions questionnaire (EQ-5D), the McGill Pain Questionnaire, and the interference score of the BPI being the measures used most often [14,178]. It is, however, important to take into account the specific disease manifestations a patient has, disease severity at the time of treatment initiation, and age when assessing QoL scores.

ERT is a prolonged treatment involving biweekly intravenous infusions. Possible concomitant adverse effects can be minimized by adopting appropriate preventative measures (e.g. reducing the infusion rate) and using pre-infusion medications if required, and can therefore by itself have a negative effect on QoL [8,115,179]. On the other hand, ERT can reduce pain in paediatric and adult patients [33,113] which can positively impact on QoL. Furthermore, paediatric patients benefit from ERT by showing increased energy levels and physical activity and reductions in headache, pain, and GI pain [180]. Most studies on the effect of ERT on QoL have been inconclusive, although home therapy for ERT has been shown to improve QoL [181,182], and a registry study that included 71 male and 59 female patients with Fabry disease also demonstrated improved QoL after 2 years of ERT [152].

In general, therapeutic goals for QoL include optimal management of pain and GI symptoms and reduction of disease-associated morbidity due to target organ damage to achieve improved QoL.

9. Discussion and concluding remarks

The therapeutic goals in this review represent the consensus from a European panel of experts and knowledge from recent clinical studies. It is hoped that these goals will help establish an individualized approach to the management of patients with Fabry disease. The goals presented in this paper are intended to be used in conjunction with the consensus recommendations on best practice management of patients with Fabry disease with ERT [183,184]. Moreover, it is important
that as our understanding of the disease and its treatment progresses, these therapeutic goals are revised as part of an ongoing process to optimize patient management.

Fabry disease is characterized by progressive, multi-organ pathology manifesting as a range of clinical phenotypes affecting both genders [1]. The aim of treatment is not only to slow or stop the progression of the disease and restore QoL, but also to reverse Fabry pathology, minimizing the disease-associated morbidity and ultimately prolonging survival. There is increasing evidence that early initiation of ERT optimizes treatment benefits, and can potentially prevent or delay progression to permanent organ damage. Unfortunately, ERT evidence for many of the typical Fabry disease-related complications such as cerebrovascular disease or hearing loss is limited due to poor monitoring.

The general therapeutic goal for optimizing patient management in Fabry disease should be to optimize both disease-specific and non-specific adjunctive treatments to prevent/minimize effects of organ damage (e.g. kidney dysfunction) and prevent clinical events (e.g. stroke) as well as control symptoms, such as neuropathic pain. The mainstay of disease-specific therapy for all Fabry patients with α-galactosidase deficiency is replacement with the deficient enzyme (ERT with either agalsidase beta or agalsidase alfa). Additionally, new therapies have recently been approved for treatment for patients with certain genetic variants responsive to chaperone stabilization of α-galactosidase [1,185–187].

Setting up a medical care plan for Fabry disease should involve the establishment of appropriate, individualized patient therapeutic goals, based on an initial assessment of affected organs, and regular monitoring and adjustment of these goals (Figure 1). Patient management should be optimized across all areas associated with Fabry disease. This can be achieved by:

- Choosing the optimal treatment strategy for the patient’s Fabry-related clinical signs and symptoms combining the timely use of ERT with appropriate non-specific adjunctive therapies (e.g. ACEi or ARB or pain control agents);
- Understanding the reasons that may underlie inter-patient differences in treatment responses (facilitating adjusting of treatment plan to improve outcomes);
- Addressing any therapy-related patient burden (e.g. consideration of home infusions) and improving patient QoL, which is often impaired even in early-stage disease because of neuropathic pain;
- Ensuring interdisciplinary communication across the specialties managing different organ complications (e.g. cardiology, nephrology, neurology); and
- Including an over-arching strategy to control pain and psychological issues such as depression/anxiety.
Despite being treated with an approved dose of ERT, some patients show disease progression in association with persistently elevated levels of plasma GL-3/lyso-GL-3. This may be due to the type or dose of ERT [91,188], the inhibitory effect of anti-agalsidase IgG antibodies (seroconversion) [189,190], insufficient time for treatment response, different responses of various disease manifestations to ERT, a reduced response to ERT in later-stage disease or as disease progresses, and lack of consistency/disagreement on the best method with which to monitor response (plasma GL-3 vs lyso-GL-3 vs urine GL-3). In view of these issues, important future research topics should include the investigation of the differential responses to treatment in different disease manifestations (for example, for the occurrence and recurrence of stroke), identification of objective measures to make assessment of the response rate more accurate (i.e. evaluating the role of renal biopsies and other, non-invasive, biomarkers of disease progression), and the effect of seroconversion and IgG antibody production on treatment response. Patients with classical Fabry disease are most likely to develop antibodies to ERT. Antibodies may negatively impact GL-3 clearance; however, due to the lack of standardized assays, the impact of anti-ERT IgG antibodies on clinical outcomes and disease progression is still controversial and needs to be further clarified [191]. ERT can be successfully reinstated in patients with Fabry disease who developed antibodies or skin test reactivity [192].

The elucidation of the appropriate dosage of ERT is another question that demands further study. It is described that, at the respective registered doses, agalsidase beta treatment leads to better clinical outcomes than agalsidase alfa [4,31,90,188]. Furthermore, the largest head-to-head trial published to date reported a higher percentage of patients with a composite clinical endpoint in the agalsidase alfa cohort compared with the agalsidase beta cohort, however differences were not statistically significant due to limited power [72]. Therefore, the finding that better outcomes are achieved with agalsidase beta compared with agalsidase alfa should be validated in adequately powered head-to-head clinical studies.

Furthermore, although the evidence regarding the newly approved chaperone therapy is growing [185,193], there is no published long-term data available. One future perspective for Fabry disease therapy includes substrate reduction therapy through the selective inhibition of glucosylceramide synthase, which has shown promise in preclinical studies [194]. The use of lipid nanoparticles in gene therapy may also provide treatment alternatives for patients with lysosomal storage disorders, including Fabry disease [195].
Figure 1. Fabry medical care: patient management algorithm.

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