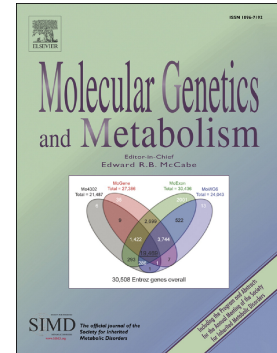# Accepted Manuscript

European expert consensus statement on therapeutic goals in Fabry disease

Christoph Wanner, Michael Arad, Ralf Baron, Alessandro Burlina, Perry M. Elliott, Ulla Feldt-Rasmussen, Victor V. Fomin, Dominique P. Germain, Derralynn A. Hughes, Ana Jovanovic, Ilkka Kantola, Aleš Linhart, Renzo Mignani, Lorenzo Monserrat, Mehdi Namdar, Albina Nowak, João-Paulo Oliveira, Alberto Ortiz, Maurizio Pieroni, Marco Spada, Anna Tylki-Szymańska, Camilla Tøndel, Miguel Viana-Baptista, Frank Weidemann, Max J. Hilz

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European expert consensus statement on therapeutic goals in Fabry disease

Christoph Wanner[a]*, Michael Arad[b], Ralf Baron[c], Alessandro Burlina[d], Perry M. Elliott[e], Ulla Feldt-Rasmussen[f], Victor V. Fomin[g], Dominique P. Germain[h], Derralynn A. Hughes[i], Ana Jovanovic[j], Ilkka Kantola[k], Aleš Linhart[l], Renzo Mignani[m], Lorenzo Monserrat[n], Mehdi Namdar[o], Albina Nowak[p], João-Paulo Oliveira[q], Alberto Ortiz[r], Maurizio Pieroni[s], Marco Spada[t], Anna Tylki-Szymańska[u], Camilla Tøndel[v], Miguel Viana-Baptista[w], Frank Weidemann[x], Max J. Hilz[y]

[a] Division of Nephrology, University Clinic, University of Würzburg, Würzburg, Germany

[b] Leviev Heart Center, Sheba Medical Center, Tel Hashomer, and Tel Aviv University, Israel

[c] Division of Neurological Pain Research and Therapy, Department of Neurology, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

[d] Neurological Unit, St Bassiano Hospital, Bassano del Grappa, Italy

[e] University College London and Barts Heart Centre, London, United Kingdom

[f] Department of Medical Endocrinology, Section 2132, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[g] I.M. Sechenov First Moscow State Medical University, Department of Internal Diseases No.1, Moscow, Russian Federation

[h] French Referral Center for Fabry disease, Division of Medical Genetics and INSERM U1179, University of Versailles, Paris-Saclay University, Montigny, France

[i] Lysosomal Storage Disorders Unit, Department of Haematology, Royal Free London NHS Foundation Trust and University College London, United Kingdom

[j] Mark Holland Metabolic Unit, Salford Royal NHS Foundation Trust, Salford, United Kingdom

[k] Division of Medicine, Turku University Hospital, Turku, Finland

[l] Second Department of Medicine – Department of Cardiovascular Medicine, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[m] Department of Nephrology, Infermi Hospital, Rimini, Italy

[n] Health in Code, A Coruña, Spain

[o] Service de Cardiologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland

[p] University Heart Center, University Hospital of Zurich and University of Zurich, Zurich, Switzerland

[q] Department of Genetics, São João Hospital Centre & Faculty of Medicine and "Instituto de Investigação e Inovação em Saúde (i3S)", University of Porto, Porto, Portugal

[r] Unidad de Diálisis, IIS-Fundación Jiménez Díaz/UAM, IRSIN and REDINREN, Madrid, Spain

[s] Cardiovascular Department, San Donato Hospital, Arezzo, Italy

[t] Department of Paediatrics, University of Torino, Torino, Italy

[u] Department of Paediatrics, Nutrition and Metabolic Diseases, Children's Memorial Health Institute, Warsaw, Poland

[v] Department of Paediatrics, Haukeland University Hospital and Department of Clinical Medicine, University of Bergen, Bergen, Norway

[w] Serviço de Neurologia, Hospital Egas Moniz, Centro Hospitalar de Lisboa Ocidental; CEDOC Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal

[x] Department of Cardiology, Innere Klinik II, Katharinen-Hospital, Unna, Germany

[y] Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

*Corresponding author at:

Division of Nephrology, University Clinic, University of Würzburg

Oberdürrbacherstr. 6, 97080 Würzburg, Germany

+49 931 20139030

E-mail address: Wanner_C@ukw.de

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.

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, mucopolysaccharidosis, 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):

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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.

4.1 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]).

4.2 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.

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

Patient subgroup	Therapeutic goals
	[52,54–56] and modification of other cardiovascular risk factors

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 $\leq$1–3 mL/min/1.73m^2/year [86], as a loss of up to 1 ml/min/1.73m^2/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/1.73m^2 and is considered fast when the rate of progression is > 5 mL/min/1.73m^2 [84,87]. A response to treatment will reduce the annual slope loss to <3 ml/min/1.73m^2. For patients with fast renal progression, slowing the process to <5 mL/min/1.73m^2/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.

Patient subgroup	Therapeutic goals
eGFR (mL/min/1.73m[2])	
No kidney involvement[a]	• eGFR should be maintained in an age-appropriate normal range[a] [87]. Avoid eGFR loss
Mild kidney involvement, eGFR at normal levels[a] or hyperfiltration (eGFR >90 ml/min/1.73m[2])	• eGFR should be maintained in an age-appropriate normal range[a] [87].
Mild-to-moderate kidney function impairment, mild eGFR decreases (eGFR 60–90 ml/min/1.73m[2])	• Prevent progression of eGFR loss and stabilize eGFR level
Moderate-to-severe kidney function impairment, mild-to-moderate eGFR decreases (eGFR 45–59 ml/min/1.73m[2])	• Prevent progression of eGFR loss to delay/avoid ESKD
Moderate-to-severe eGFR decreases (eGFR 30–44 ml/min/1.73m[2])	• Prevent progression of eGFR loss to delay/avoid ESKD
Severe eGFR decreases (eGFR 15–29 ml/min/1.73m[2])	• Decrease the slope of eGFR as much as possible; delay the progression to ESKD
ESKD	• 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
Albuminuria (mg/g)	
General: all patients	• Keep albuminuria levels as low as possible
Mild-to-moderate kidney function impairment; albuminuria levels:	• Normalize/stabilize albuminuria

<30 mg/g (<3 mg/mmol)	
Albuminuria levels: 30–300 mg/g (3–30 mg/mmol)	• Normalize/stabilize albuminuria
Albuminuria levels: >300 mg/g (>30 mg/mmol)	• Reduce levels to <300 mg/g (30 mg/mmol)
Moderate-to-severe kidney function impairment	• Slow progression of albuminuria

CNS, central nervous system; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; [a] A normal level usually refers to eGFR 90–120 ml/min/1.73m^2 [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 dysaesthesias, 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.

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

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.

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

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, retro-cochlea, 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.

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

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.

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

* 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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┌─────────────────────────────────────────────────┐
│         Confirmed diagnosis of Fabry disease      │
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                        ↓
┌─────────────────────────────────────────────────┐
│   Comprehensive initial patient assessment for organ │
│     pathology and Fabry clinical signs and symptoms  │
└─────────────────────────────────────────────────┘
                        ↓
┌─────────────────────────────────────────────────┐
│        Establish appropriate therapeutic goals     │
└─────────────────────────────────────────────────┘
                        ↓
┌─────────────────────────────────────────────────┐
│    Determine the most appropriate treatment plan   │
│  (discuss and agree with the patient and their family/carers if │
│                 paediatric patient)                │
└─────────────────────────────────────────────────┘
                        ↓
┌─────────────────────────────────────────────────┐
│  Assess patient's clinical status through regular monitoring │
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│           Therapeutic goals achieved?              │
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            ↙                          ↘
┌──────────────────────┐    ┌──────────────────────┐
│        YES            │    │         NO           │
│ Maintain treatments* and │  │ Review and optimize  │
│ reassess clinical status │  │ therapeutic goals and/or │
│  through continued    │    │  treatments*, and reassess │
│    monitoring         │    │    clinical status   │
└──────────────────────┘    └──────────────────────┘
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*disease-specific treatment and/or concomitant therapies

Disclosures

Conflicts of Interest

- Christoph Wanner has received research support from Sanofi Genzyme; is a consultant for Actelion Pharmaceuticals, Protalix, Boehringer Ingelheim, and Sanofi Genzyme; is a member of the European Advisory Board of the Fabry Registry.
- Michael Arad has received travel support from Sanofi Genzyme and Shire.
- Ralf Baron has received speaker honoraria from Astellas, Bayer-Schering, Boehringer Ingelheim Pharma , Desitin, Eisai, Grünenthal, Lilly, Medtronic Inc. Neuromodulation, MSD,

Mundipharma, Pfizer, Sanofi Genzyme, Sanofi Pasteur, Seqirus, Teva Pharma; has been a consultant for AbbVie, Allergan, Astellas, AstraZeneca, Biogen Idec, Boehringer Ingelheim Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, Galapagos, Genentech, Glenmark Pharmaceuticals, Grünenthal, Lilly, Medtronic, Merck, Mundipharma, Novartis, Pfizer, Sanofi Genzyme, Sanofi Pasteur, Seqirus, Teva Pharma; has received research/grant support from AbbVie, Grünenthal, Mundipharma, Pfizer, Sanofi Genzyme, and; member of the EU Project No. 633491: DOLORisk; member of the IMI "Europain" collaboration, industry members of which are: AstraZeneca, Boehringer Ingelheim Pharma, Esteve, Eli Lilly, Grünenthal, Pfizer, Sanofi Aventis, UCB-Pharma, and; German Federal Ministry of Education and Research (BMBF); member of the ERA_NET NEURON/IM-PAIN Project (01EW1503), German Research Network on Neuropathic Pain (01EM0903), NoPain system biology (0316177C), and German Research Foundation (DFG).

- Alessandro Burlina has received speaker honoraria and travel support from Amicus Therapeutics and Sanofi Genzyme; is a member of the European Advisory Board of the Fabry Registry.

- Perry M. Elliott has received speaker honoraria from Shire; has received consultancy and speaker honoraria from Gilead Sciences., MyoKardia, Pfizer, and Sanofi Genzyme.

- Ulla Feldt-Rasmussen has received speaker and advisory board honoraria from Amicus Therapeutics, Sanofi, Sanofi Genzyme, and Shire; has received unrestricted research grants from Sanofi Genzyme and Shire; is a member of the European Advisory Board of the Fabry Registry and the Nordic and International Advisory Boards of Amicus Therapeutics.

- Victor V. Fomin has received speaker honoraria and travel support from Novartis and Sanofi Genzyme.

- Dominique P. Germain is a consultant for Sanofi Genzyme and Shire; has received research support from Sanofi Genzyme and Shire; and has received speaker honoraria and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire.

- Derralynn A. Hughes has received speaker and advisory board honoraria, travel support and research support from Amicus Therapeutics, Protalix, Sanofi Genzyme and Shire.

- Ana Jovanovic has received travel support from Amicus Therapeutics, Biomarin, Sanofi Genzyme and Shire, has received speaker and advisory board honoraria from Amicus Therapeutics, Sanofi Genzyme and Shire.

- Ilkka Kantola has received speaker honoraria and travel support from Sanofi Genzyme and Shire.

- Aleš Linhart is a consultant for Amicus Therapeutics, Sanofi Genzyme, and Shire; has received speaker honoraria and travel support from Sanofi Genzyme and Shire.

- Renzo Mignani has received speaker and advisory board honoraria, and travel support from Sanofi Genzyme.

- Lorenzo Monserrat has received speaker honoraria and travel support from Sanofi Genzyme and Shire; is a shareholder of Health in Code SL.

- Mehdi Namdar has received research support, advisory board attendance and speaker honoraria, and travel support from Sanofi Genzyme and has received research support from Shire.
- Albina Nowak is a consultant for Shire; has received speaker honoraria, travel support and research support from Sanofi Genzyme and Shire.
- João-Paulo Oliveira has received consulting honoraria, and unrestricted research grants and funding for research projects from Sanofi Genzyme; has received speaker honoraria from Sanofi Genzyme and Shire; has received conference and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire; is a member of the European Advisory Board of the Fabry Registry.
- Alberto Ortiz has received speaker honoraria from Amicus Therapeutics, Sanofi Genzyme and Shire; has received consulting honoraria, and conference and travel support from Sanofi Genzyme; is a member of the European Advisory Board of the Fabry Registry.
- Maurizio Pieroni has received advisory board honoraria from Amicus Therapeutics and Sanofi Genzyme; has receivedspeaker honoraria from Amicus Therapeutics, Sanofi Genzyme and Shire.
- Marco Spada has received speaker and advisory board honoraria, and travel support from Sanofi Genzyme and Shire.
- Anna Tylki-Szymańska has received speaker honoraria from Sanofi Genzyme and Shire; is a member of the European Advisory Board of the Fabry Registry.
- Camilla Tøndel has received speaker honoraria and travel support from Sanofi Genzyme and Shire; has participated in studies supported by Protalix, Sanofi Genzyme, and Shire; is a member of the European Advisory Board of the Fabry Registry.
- Miguel Viana-Baptista has received consulting honoraria, speaker honoraria, conference and travel support, and unrestricted research grants and funding for research projects from Sanofi Genzyme; has received consulting and speaker honoraria from Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer-Bristol Myers-Squibb Portugal; has received conference and travel support from Boehringer Ingelheim; is a member of the Global Neurological Fabry Disease Advisory Board.
- Frank Weidemann has received speaker honoraria and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire; has received research support from Sanofi Genzyme and Shire; is a member of the European Advisory Board of the Fabry Registry.
- Max J. Hilz has received research/grant support from Bayer Health Care and Novartis Pharma; has received speaker honoraria and travel support from Sanofi Genzyme.

References

[1]   Germain, DP, Fabry disease. Orphanet J. Rare Dis. 5 (2010) 30. doi: 10.1186/1750-1172-5-30.

[2]   De Francesco PN, Mucci JM, Ceci R, Fossati CA, Rozenfeld PA, Fabry disease peripheral blood immune cells release inflammatory cytokines: role of globotriaosylceramide. Mol. Genet. Metab. 109 (2013) 93-9. doi: 10.1016/j.ymgme.2013.02.003.

[3]   Elliot PM, Germain DP, Hilz MJ, et al., Evaluation of the value of systematic reviews in rare diseases using Fabry disease as an exemplar [Molec Genet Metab, 2017, submitted].

[4]   Germain DP, Elliott PM, Falissard B,et al., The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease – a systematic literature review by a European panel of experts [Molec Genet Metab, 2017, submitted].

[5]   Germain DP, Arad M, Burlina A, et al., The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease – a systematic literature review by a European panel of experts[Molec Genet Metab, 2017, submitted].

[6]   Spada M, et al. Baron R, Elliot PM, The effect of enzyme replacement therapy on clinical outcomes in paediatric [female] patients with Fabry disease – a systematic literature review by a European panel of experts [Molec Genet Metab, 2017, submitted].

[7]   Rombach SM, Aerts JM, Poorthuis BJ, et al., Long-term effect of antibodies against infused alpha-galactosidase A in Fabry disease on plasma and urinary (lyso)Gb3 reduction and treatment outcome. PLoS One. 7 (2012) e47805. doi: 10.1371/journal.pone.0047805.

[8]   Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A--replacement therapy in Fabry's disease. N Engl J Med. 2001;345:9-16.

[9]   Schiffmann R, Kopp JB, Austin HA 3rd, et al., Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 285 (2001) 2743–2749.

[10]   Wilcox WR, Banikazemi M, Guffon N, et al., Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am. J. Hum. Genet. 75 (2004) 65–74.

[11]   Germain DP, Charrow J, Desnick RJ, et al.; International Fabry Disease Study Group. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J. Med. Genet. 52 (2015) 353–358.

[12]   Niemann M, Rolfs A, Störk S, et al., Gene mutations versus clinically relevant phenotypes: lyso-Gb3 defines Fabry disease. Circ. Cardiovasc. Genet. 7 (2014) 8–16. doi: 10.1161/CIRCGENETICS.113.000249.

[13]   Aerts JM, Groener JE, Kuiper S, et al., Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc. Natl. Acad. Sci. U S A. 105 (2008) 2812–2817. doi: 10.1073/pnas.0712309105.

[14]   Goker-Alpan O, Longo N, McDonald M, et al., An open-label clinical trial of agalsidase alfa enzyme replacement therapy in children with Fabry disease who are naïve to enzyme replacement therapy. Drug Des. Devel. Ther. 10 (2016) 1771–1781. doi: 10.2147/DDDT.S102761. eCollection 2016.

[15] Smid BE, Rombach SM, Aerts JM, et al., Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients. Orphanet J. Rare Dis. 6 (2011) 69. doi: 10.1186/1750-1172-6-69.

[16] Smid BE, van der Tol L, Biegstraaten M, Linthorst GE, Hollak CE, Poorthuis BJ, Plasma globotriaosylsphingosine in relation to phenotypes of Fabry disease. J. Med. Genet. 52 (2015) 262–268. doi: 10.1136/jmedgenet-2014-102872.

[17] Goker-Alpan O, Gambello MJ, Maegawa GH, et al., Reduction of plasma globotriaosylsphingosine levels after switching from agalsidase alfa to agalsidase beta as enzyme replacement therapy for Fabry disease. JIMD Rep. 25 (2015) 96–106.

[18] Kitagawa T, Ishige N, Suzuki K, et al., Non-invasive screening method for Fabry disease by measuring globotriaosylceramide in whole urine samples using tandem mass spectrometry. Mol. Genet. Metab. 85 (2005) 196–202.

[19] van Breemen MJ, Rombach SM, Dekker N, Poorthuis BJ, Linthorst GE, Zwinderman AH, Breunig F, Wanner C, Aerts JM, Hollak CE, Reduction of elevated plasma globotriaosylsphingosine in patients with classic Fabry disease following enzyme replacement therapy, Biochim. Biophys. Acta 1812 (2011) 70–76.

[20] Young E, Mills K, Morris P, et al., Is globotriaosylceramide a useful biomarker in Fabry disease? Acta Paediatr. 94 (2005) 51–4; discussion 37–38.

[21] Vedder AC, Linthorst GE, Houge G, et al., Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. PLoS One. 2 (2007) e598.

[22] Vedder AC, Breunig F, Donker-Koopman WE, et al., Treatment of Fabry disease with different dosing regimens of agalsidase: effects on antibody formation and GL-3. Mol. Genet. Metab. 94 (2008) 319–325. doi: 10.1016/j.ymgme.2008.03.003.

[23] Ohashi T, Sakuma M, Kitagawa T, Suzuki K, Ishige N, Eto Y, Influence of antibody formation on reduction of globotriaosylceramide (GL-3) in urine from Fabry patients during agalsidase beta therapy. Mol. Genet. Metab. 92 (2007) 271–273.

[24] Ferreira S, Auray-Blais C, Boutin M, et al., Variations in the GLA gene correlate with globotriaosylceramide and globotriaosylsphingosine analog levels in urine and plasma. Clin. Chim. Acta. 447 (2015) 96–104. doi: 10.1016/j.cca.2015.06.003.

[25] Tøndel C, Bostad L, Hirth A, Svarstad E, Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria. Am. J. Kidney Dis. 51 (2008) 767–776. doi: 10.1053/j.ajkd.2007.12.032.

[26] Tøndel C, Kanai T, Larsen K, et al., Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria. Nephron. 129 (2015) 16–21. doi: 10.1159/000369309.

[27] Kim JH, Lee BH, Hyang Cho J, et al. Long-term enzyme replacement therapy for Fabry disease: efficacy and unmet needs in cardiac and renal outcomes. J. Hum. Genet. 61 (2016) 923–929. doi: 10.1038/jhg.2016.78.

[28]   Wijburg FA, Bénichou B, Bichet DG, et al., Characterization of early disease status in treatment-naive male paediatric patients with Fabry disease enrolled in a randomized clinical trial. PLoS One. 10 (2015) e0124987. doi: 10.1371/journal.pone.0124987.

[29]   Najafian B, Svarstad E, Bostad L, et al., Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. Kidney Int. 79 (2011) 663–670. doi: 10.1038/ki.2010.484.

[30]   Tøndel C, Vikse BE, Bostad L, Svarstad E, Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 1988–2010. Clin. J. Am. Soc. Nephrol. 7 (2012) 1591–1597. doi: 10.2215/CJN.02150212.

[31]   Tøndel C, Bostad L, Larsen KK, et al., Agalsidase benefits renal histology in young patients with Fabry disease. J. Am. Soc. Nephrol. 24 (2013) 137–148. doi: 10.1681/ASN.2012030316.

[32]   Skrunes R, Svarstad E, Kampevold Larsen K, Leh S, Tøndel C, Re-accumulation of globotriaosylceramide in podocytes after agalsidase dose reduction in young Fabry patients. Nephrol. Dial. Transplant. 32 (2017) 807–813. doi: 10.1093/ndt/gfw094.

[33]   Germain DP, Waldek S, Banikazemi M, et al., Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. J. Am. Soc. Nephrol. 18 (2007) 1547–1557.

[34]   Thurberg BL, Rennke H, Colvin RB, et al., Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int. 62 (2002) 1933–1946.

[35]   Lubanda JC, Anijalg E, Bzdúch V, Thurberg BL, Bénichou B, Tylki-Szymanska A, Evaluation of a low dose, after a standard therapeutic dose, of agalsidase beta during enzyme replacement therapy in patients with Fabry disease. Genet. Med. 11 (2009) 256–264. doi: 10.1097/GIM.0b013e3181981d82.

[36]   Najafian B, Tøndel C, Svarstad E, Sokolovkiy A, Smith K, Mauer M, One year of enzyme replacement therapy reduces globotriaosylceramide inclusions in podocytes in male adult patients with Fabry disease. PLoS One. 15 (2016) e015282. doi:10.1371/journal.pone.0152812.

[37]   Kampmann C, Baehner F, Whybra C, et al., Cardiac manifestations of Anderson-Fabry disease in heterozygous females. J. Am. Coll. Cardiol. 40 (2002) 1668–1674.

[38]   Kampmann C, Linhart A, Baehner F, et al., Onset and progression of the Anderson-Fabry disease related cardiomyopathy. Int. J. Cardiol. 130 (2008) 367–373. doi: 10.1016/j.ijcard.2008.03.007.

[39]   Krämer J, Niemann M, Störk S, et al., Relation of burden of myocardial fibrosis to malignant ventricular arrhythmias and outcomes in Fabry disease. Am. J. Cardiol. 144 (2014) 895–900. doi: 10.1016/j.amjcard.2014.06.019.

[40]   Senechal M, Germain DP, Fabry disease: a functional and anatomical study of cardiac manifestations in 20 hemizygous male patients. Clin. Genet. 63 (2003) 46–52.

[41]   Shah JS, Hughes DA, Sachdev B, et al., Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. Am. J. Cardiol. 96 (2005) 842–846.

[42]   Patel MR, Cecchi F, Cizmarik M, et al., Cardiovascular events in patients with Fabry disease natural history data from the Fabry registry. J. Am. Coll. Cardiol. 57 (2011) 1093–1099. doi: 10.1016/j.jacc.2010.11.018.

[43]   Patel V, O'Mahony C, Hughes D, et al., Clinical and genetic predictors of major cardiac events in patients with Anderson-Fabry disease. Heart. 101 (2015) 961–966. doi: 10.1136/heartjnl-2014-306782.

[44]   Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P, Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet. Med. 11 (2009) 790–796. doi: 10.1097/GIM.0b013e3181bb05bb.

[45]   Elliott PM, Anastasakis A, Borger MA, et al., 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur. Heart J. 35 (2014) 2733–2779. doi: 10.1093/eurheartj/ehu284.

[46]   Linhart A, Kampmann C, Zamorano JL, et al.; European FOS Investigators. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur. Heart J. 28 (2007) 1228–1235.

[47]   Acharya D, Doppalapudi H, Tallaj JA, Arrhythmias in Fabry cardiomyopathy. Card. Electrophysiol. Clin. 7 (2015) 283–291. doi: 10.1016/j.ccep.2015.03.014.

[48]   Motwani M, Banypersad S, Woolfson P, Waldek S, Enzyme replacement therapy improves cardiac features and severity of Fabry disease. Mol. Genet. Metab. 107 (2012) 197–202. doi: 10.1016/j.ymgme.2012.05.011.

[49]   Ortiz A, Abiose A, Bichet DG, et al., Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: data from the Fabry Registry. J Med. Genet. 53 (2016) 495–502. doi: 10.1136/jmedgenet-2015-103486.

[50]   Weidemann F, Niemann M, Störk S, et al., Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications. J. Intern. Med. 274 (2013) 331–341. doi: 10.1111/joim.12077.

[51]   Beck M, Hughes D, Kampmann C, et al.; Fabry Outcome Survey Study Group, Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: A Fabry Outcome Survey analysis. Mol. Genet. Metab. Rep. 3 (2015) 21–27. doi: 10.1016/j.ymgmr.2015.02.002.

[52]   Krämer J, Nordbeck P, Störk S, et al., Electrical changes in resting, exercise, and Holter electrocardiography in Fabry cardiomyopathy. JMID Rep. (2015) [Epub ahead of print]. doi: 10.1007/8904_2015_502 .

[53]   Ponikowski P, Voors AA, Anker SD, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 18 (2016) 891–975. doi: 10.1002/ejhf.592

[54] James PA, Oparil S, Carter BL, et al.; 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 311 (2014) 507–520. doi: 10.1001/jama.2013.284427.

[55] Krämer J, Bijnens B, Störk S, et al., Left ventricular geometry and blood pressure as predictors of adverse progression of Fabry cardiomyopathy. PLoS One. 10 (2015) e0140627. doi: 10.1371/journal.pone.0140627.

[56] Mancia G, Fagard R, Narkiewicz K, et al.; Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology, 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press. 23 (2014) 3–16. doi: 10.3109/08037051.2014.868629.

[57] Weidemann F, Breunig F, Beer M, et al., Improvement of Cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. Circulation. 108 (2003) 1299–1301.

[58] Hughes DA, Elliott PM, Shah J, et al., Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart. 94 (2008) 153–158.

[59] Mehta A, Beck M, Elliott P, et al.; Fabry Outcome Survey investigators, Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet. 374 (2009) 1986–1996. doi: 10.1016/S0140-6736(09)61493-8.

[60] Weidemann F, Niemann M, Breunig F, et al.; Fabry Outcome Survey Investigators, Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation. 119 (2009) 524–529. doi: 10.1161/CIRCULATIONAHA.108.794529.

[61] Germain DP, Weidemann F, Abiose A, et al.; Fabry Registry, Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: data from the Fabry Registry. Genet. Med. 15 (2013) 958–965. doi: 10.1038/gim.2013.53.

[62] Schmied C, Nowak A, Gruner C, et al., The value of ECG parameters as markers of treatment response in Fabry cardiomyopathy. Heart. 102 (2016) 1309–1314. doi: 10.1136/heartjnl-2015-308897.

[63] Seydelmann N, Wanner C, Störk S, Ertl G, Weidemann F, Fabry disease and the heart. Best Pract. Res. Clin. Endocrinol. Metab. 29 (2015) 195–204. doi: 10.1016/j.beem.2014.10.003.

[64] Niemann M, Hermann S, Hu K, et al., Differences in Fabry cardiomyopathy between female and male patients. JACC Cardiovasc Imaging. 4 (2011) 592–601. doi: 10.1016/j.jcmg.2011.01.020.

[65] Takenaka T, Teraguchi H, Yoshida A, et al., Terminal stage cardiac findings in patients with cardiac Fabry disease: an electrocardiographic, echocardiographic, and autopsy study. J. Cardiol. 51 (2008) 50–9. doi: 10.1016/j.jjcc.2007.12.001.

[66] Weidemann F, Breunig F, Beer M, et al., The variation of morphological and functional cardiac manifestation in Fabry disease: potential implications for the time course of the disease. Eur. Heart J. 26 (2005) 1221–1227.

[67]   Acharya D, Robertson P, Kay GN, et al., Arrhythmias in Fabry cardiomyopathy. Clin. Cardiol. 35 (2012) 738–740. doi: 10.1002/clc.22047.

[68]   Weidemann F, Maier SK, Störk S, et al., Usefulness of an implantable loop recorder to detect clinically relevant arrhythmias in patients with advanced Fabry cardiomyopathy. Am. J. Cardiol 118 (2016) 264–274. doi: 10.1016/j.amjcard.2016.04.033.

[69]   Coats CJ, Heywood WE, Mills K, Elliott PM, Current applications of biomarkers in cardiomyopathies. Expert Rev. Cardiovasc. Ther. 13 (2015) 825–837. doi: 10.1586/14779072.2015.1053873.

[70]   Seydelman N, Lui D, Kramer JH, et al., High-sensitivity troponin: a clinical blood biomarker for staging cardiomyopathy in Fabry disease. J. Am. Heart. Assoc. 5 (2016) e002839. doi: 10.1161/JAHA.115.002839.

[71]   Kampmann C, Perrin A, Beck M, Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment. Orphanet J. Rare Dis. 10 (2015) 125. doi: 10.1186/s13023-015-0338-2.

[72]   Sirrs SM, Bichet DG, Casey R, et al.; CFDI investigators, Outcomes of patients treated through the Canadian Fabry disease initiative. Mol. Genet. Metab. 111 (2014) 499–506. doi: 10.1016/j.ymgme.2014.01.014.

[73]   Banikazemi M, Bultas J, Waldek S, et al.; Fabry Disease Clinical Trial Study Group, Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann. Intern. Med. 146 (2007) 77–86.

[74]   Eng CM, Germain DP, Banikazemi M, et al., Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet. Med. 9 (2006) 539–548.

[75]   De Rivas B, Barrios V, Redón J, Calderón A, Effectiveness of an Interventional Program to Improve Blood Pressure Control in Hypertensive Patients at High Risk for Developing Heart Failure: HEROIC study. J. Clin. Hypertens. (Greenwich). 12 (2010) 335–344. doi: 10.1111/j.1751-7176.2010.00271.x.

[76]   Kannan A, Janardhanan R, Hypertension as a risk factor for heart failure. Curr. Hypertens. Rep. 16 (2014) 447. doi: 10.1007/s11906-014-0447-7.

[77]   Warnock DG, Ortiz A, Mauer M, et al.; Fabry registry, Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. Nephrol. Dial. Transplant. 27 (2012) 1042–1049. doi: 10.1093/ndt/gfr420.

[78]   Ortiz A, Oliveira JP, Waldek S, Warnock DG, Cianciaruso B, Wanner C; Fabry Registry, Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. Nephrol. Dial. Transplant. 23 (2008) 1600–1607. doi: 10.1093/ndt/gfm848.

[79]   Feriozzi S, Torras J, Cybulla M, Nicholls K, Sunder-Plassmann G, West M; FOS Investigators, The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy. Clin. J. Am. Soc. Nephrol. 7 (2012) 60–69. doi: 10.2215/CJN.03130411.

[80]   Warnock DG, Thomas CP, Vujkovac B, et al., Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy. J. Med. Genet. 52 (2015) 860–866.

[81]   Tahir H, Jackson LL, Warnock DG. Antiproteinuric therapy and Fabry nephropathy: sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-beta. J. Am. Soc. Nephrol. 18 (2007) 2609–2617.

[82]   Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), A new equation to estimate glomerular filtration rate. Ann. Intern. Med. 150 (2009) 604–612.

[83]   Schwartz GJ, Muñoz A, Schneider MF, et al., New equations to estimate GFR in children with CKD. J. Am. Soc. Nephrol. 20 (2009) 629–637. doi: 10.1681/ASN.2008030287.

[84]   Tøndel C, Ramaswami U, Aakre KM, Wijburg F, Bouwman M, Svarstad E, Monitoring renal function in children with Fabry disease: comparisons of measured and creatinine-based estimated glomerular filtration rate. Nephrol. Dial. Transplant. 25 (2010) 1507–1513. doi: 10.1093/ndt/gfp658.

[85]   Schiffmann R, Warnock DG, Banikazemi M, et al., Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant. 24 (2009)2102–2111. doi: 10.1093/ndt/gfp031.

[86]   Wanner C, Oliveira JP, Ortiz A, et al., Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. Clin. J. Am. Soc. Nephrol. 5 (2010) 2220–2228. doi: 10.2215/CJN.04340510.

[87]   Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. Suppl. 3 (2013) 1–150. www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.

[88]   Mignani R, Feriozzi S, Schaefer RM, et al., Dialysis and transplantation in Fabry disease: indications for enzyme replacement therapy. Clin. J. Am. Soc. Nephrol. 5 (2010) 379–3785. doi: 10.2215/CJN.05570809.

[89]   Prabakaran T, Birn H, Bibby BM, et al., Long-term enzyme replacement therapy is associated with reduced proteinuria and preserved proximal tubular function in women with Fabry disease. Nephrol. Dial. Transplant. 29 (2014) 619–625. doi: 10.1093/ndt/gft452.

[90]   Weidemann F, Krämer J, Duning T, et al., Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch. J. Am. Soc. Nephrol. 25 (2014) 837–849. doi: 10.1681/ASN.2013060585.

[91]   Baron R, Förster M, Binder A. Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach. Lancet Neurol. 11 (2012) 999–1005. doi: 10.1016/S1474-4422(12)70189-8.

[92]   Arends M, Wijburg FA, Wanner C, et al., Favourable effect of early versus late start of enzyme replacement therapy on plasma globotriaosylsphingosine levels in men with classical Fabry disease. Mol. Genet. Metab. 121 (2017) 157–161. doi: 10.1016/j.ymgme.2017.05.001.

[93]   Burlina AP, Sims KB, Politei JM, et al., Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. BMC Neurol. 11 (2011) 61. doi: 10.1186/1471-2377-11-61.

[94]   Politei JM, Bouhassira D, Germain DP, et al., Pain in Fabry disease: practical recommendations for diagnosis and treatment. CNS Neurosci. Ther. 22 (2016) 568–576. doi: 10.1111/cns.12542.

[95]   Maag R, Binder A, Maier C, et al., Detection of a characteristic painful neuropathy in Fabry disease: a pilot study. Pain Med. 9 (2008) 1217–1223. doi: 10.1111/j.1526-4637.2008.00470.x.

[96]   Biegstraaten M, Hollak CE, Bakkers M, Faber CG, Aerts JM, van Schaik IN, Small fiber neuropathy in Fabry disease. Mol. Genet. Metab. 106 (2012) 135–141. doi: 10.1016/j.ymgme.2012.03.010.

[97]   Üçeyler N, He L, Schönfeld D, et al., Small fibers in Fabry disease: baseline and follow-up data under enzyme replacement therapy. J. Peripher. Nerv. Syst. 16 (2011) 304–314. doi: 10.1111/j.1529-8027.2011.00365.x.

[98]   Kolodny E, Fellgiebel A, Hilz MJ, et al., Cerebrovascular involvement in Fabry disease: current status of knowledge. Stroke. 46 (2015) 302–313. doi: 10.1161/STROKEAHA.114.006283.

[99]   Sigmundsdottir L, Tchan MC, Knopman AA, Menzies GC, Batchelor J, Sillence DO, Cognitive and psychological functioning in Fabry disease. Arch. Clin. Neuropsychol. 29 (2014) 642–650. doi: 10.1093/arclin/acu047.

[100]   Bolsover FE, Murphy E, Cipolotti L, Werring DJ, Lachmann RH, Cognitive dysfunction and depression in Fabry disease: a systematic review. J. Inherit. Metab. Dis. 37 (2014) 177–187. doi: 10.1007/s10545-013-9643-x.

[101]   Ries M, Ramaswami U, Parini R, et al., The early clinical phenotype of FD: a study on 35 European children and adolescents. Eur. J. Pediatr. 162 (2003) 767–772.

[102]   Mehta A, Ricci R, Widmer U, et al., Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur. J. Clin. Invest. 34 (2004) 236–242.

[103]   Üçeyler N, Ganendiran S, Kramer D, Sommer C, Characterization of Pain in Fabry disease. Clin. J. Pain. 30 (2014) 915–920. doi: 10.1097/AJP.0000000000000041.

[104]   Salviati A, Burlina AP, Borsini W, Nervous system and Fabry disease, from symptoms to diagnosis: damage evaluation and follow-up in adult patients, enzyme replacement, and support therapy. Neurol. Sci. 31 (2010) 299–306. doi: 10.1007/s10072-009-0211-y.

[105]   Hilz MJ, Stemper B, Kolodny EH, Lower limb cold exposure induces pain and prolonged small fiber dysfunction in Fabry patients. Pain. 84 (2000) 361–365.

[106]   Hilz MJ, Brys M, Marthol H, Stemper B, Dütsch M., Enzyme replacement therapy improves function of C-, Adelta- and Abeta-nerve fibers in Fabry neuropathy. Neurology. 62 (2004) 1066–1072.

[107] Üçeyler N, Magg B, Thomas P, Wiedmann S, Heuschmann P, Sommer C, A comprehensive Fabry-related pain questionnaire for adult patients. Pain. 155 (2014) 2301–2305. doi: 10.1016/j.pain.2014.08.024.

[108] Ramaswami U, Stull DE, Parini R, et al.; FOS Investigators, Measuring patient experiences in Fabry disease: validation of the Fabry-specific Pediatric Health and Pain Questionnaire (FPHPQ). Health Qual. Life Outcomes. 10 (2012) 116. doi: 10.1186/1477-7525-10-116.

[109] Arning K, Naleschinski D, Maag R, et al., FabryScan: a screening tool for early detection of Fabry disease. J. Neurol. 259 (2012) 2393–2400. doi: 10.1007/s00415-012-6619-y.

[110] Magg B, Riegler C, Wiedmann S, Heuschmann P, Sommer C, Üçeyler N, Self-administered version of the Fabry-associated pain questionnaire for adult patients. Orphanet J. Rare. Dis. 10 (2015) 113. doi: 10.1186/s13023-015-0325-7.

[111] Ries M, Clarke JT, Whybra C, et al., Enzyme-replacement therapy with agalsidase alfa in children with Fabry disease. Pediatrics. 118 (2006) 924–932.

[112] Wraith JE, Tylki-Szymanska A, Guffon N, et al., Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. J. Pediatr. 152 (2008) 563–570. doi: 10.1016/j.jpeds.2007.09.007.

[113] Schiffmann R, Martin RA, Reimschisel T, et al., Four-year prospective clinical trial of agalsidase alfa in children with Fabry disease. J. Pediatr. 156 (2010) 832–837. doi: 10.1016/j.jpeds.2009.11.007.

[114] Anderson LJ, Wyatt KM, Henley W, et al., Long-term effectiveness of enzyme replacement therapy in Fabry disease: results from the NCS-LSD cohort study. J. Inherit. Metab. Dis. 37 (2014) 969–978. doi: 10.1007/s10545-014-9717-4.

[115] Schiffmann R, Pastores GM, Lien YH, et al., Agalsidase alfa in pediatric patients with Fabry disease: a 6.5-year open-label follow-up study. Orphanet J. Rare Dis. 9 (2014) 169. doi: 10.1186/s13023-014-0169-6.

[116] Attal N, Cruccu G, Baron R, et al.; European Federation of Neurological Societies, EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur. J. Neurol. 17 (2010) 1113-e88. doi: 10.1111/j.1468-1331.2010.02999.x.

[117] Finnerup NB, Attal N, Haroutounian S, et al., Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 14 (2015) 162–173. doi: 10.1016/S1474-4422(14)70251-0.

[118] Schuller Y, Linthorst GE, Hollak, Van Schaik IN, Biegstraaten M, Pain management strategies for neuropathic pain in Fabry disease - a systematic review. BMC Neurol. 16 (2016) 25. doi: 10.1186/s12883-016-0549-8.

[119] Ballantyne JC, Opioids for the treatment of chronic pain: mistakes made, lessons learned, and future directions. Anesth. Analg. 125 (2017) 1769–1778. doi: 10.1213/ANE.0000000000002500

[120] Ghali J, Murugasu A, Day T, Nicholls K, Carpal tunnel syndrome in Fabry disease. JIMD Rep. 2 (2012) 17–23. doi: 10.1007/8904_2011_37.

[121]   Sims K, Politei J, Banikazemi M, Lee P, Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry. Stroke. 40 (2009) 788–794. doi: 10.1161/STROKEAHA.108.526293.

[122]   Demuth K, Germain DP, Endothelial markers and homocysteine in patients with classic Fabry disease. Acta Paediatr. Suppl. 91 (2002) 57–61.

[123]   El Dib R, Gomaa H, Ortiz A, Politei J, Kapoor A, Barreto F, Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. PLoS One. 12 (2017) e0173358. doi: 10.1371/journal.pone.0173358.

[124]   Meschia JF, Bushnell C, Boden-Albala B, et al.; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension, Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 45 (2014) 3754–3832. doi: 10.1161/STR.0000000000000046.

[125]   Kernan WN, Ovbiagele B, Black HR, et al.; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease, Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 45 (2014) 2160–2236. doi: 10.1161/STR.0000000000000024.

[126]   Fellgiebel A, Gartenschläger M, Wildberger K, Scheurich A, Desnick RJ, Sims K, Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease. Cerebrovasc Dis. 38 (2014) 448–456. doi: 10.1159/000369293.

[127]   Fazekas F, Enzinger C, Schmidt R, Grittner U, Giese AK, Hennerici MG, Huber R, Jungehulsing GJ, Kaps M, Kessler C, Martus P, Putaala J, Ropele S, Tanislav C, Tatlisumak T, Thijs V, von Sarnowski B, Norrving B, Rolfs A; SIFAP 1 Investigators. Brain magnetic resonance imaging findings fail to suspect Fabry disease in young patients with an acute cerebrovascular event. Stroke. 46 (2015) 1548–1553. doi: 10.1161/STROKEAHA.114.008548

[128]   Rost NS, Cloonan L, Kanakis AS, et al., Determinants of white matter hyperintensity burden in patients with Fabry disease. Neurology. 86 (2016) 1880–1886. doi: 10.1212/WNL.0000000000002673.

[129]   Politei J, Schenone AB, Burlina A, et al., Vertebrobasilar dolichoectasia in Fabry disease: the earliest marker of neurovascular involvement? J. Inborn Errors Metab. Screen. 2014. doi: 10.1177/2326409814541246.
http://journals.sagepub.com/doi/abs/10.1177/2326409814541246?journalCode=iema.

[130]   Manara R, Carlier RY, Righetto S, et al., Basilar artery changes in Fabry disease. Am. J. Neuroradiol. 38 (2017) 531–536. doi: 10.3174/ajnr.A5069.

[131]   Segal P, Kohn Y, Pollak Y, Altarescu G, Galili-Weisstub E, Raas-Rothschild A, Psychiatric and cognitive profile in Anderson-Fabry patients: a preliminary study. J. Inherit. Metab. Dis. 33 (2010) 429–436. doi: 10.1007/s10545-010-9133-3.

[132] Löhle M, Hughes D, Milligan A, et al., Clinical prodromes of neurodegeneration in Anderson-Fabry disease. Neurology. 84 (2015) 1454–1464. doi: 10.1212/WNL.0000000000001450.

[133] Lelieveld IM, Böttcher A, Hennermann JB, Beck M, Fellgiebel A, Eight-year follow-up of neuropsychiatric symptoms and brain structural changes in Fabry disease. PLoS One. 10 (2015) e0137603. doi: 10.1371/journal.pone.0137603.

[134] Cole AL, Lee PJ, Hughes DA, Deegan PB, Waldek S, Lachmann RH, Depression in adults with Fabry disease: a common and under-diagnosed problem. J. Inherit. Metab. Dis. 30 (2007) 943–951.

[135] Germain DP, Avan P, Chassaing A, Bonfils P, Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of twenty-two hemizygous male patients. BMC Med. Genet. 3 (2002) 10.

[136] Suntjens EB, Smid BE, Biegstraaten M, Dreschler WA, Hollak CE, Linthorst GE, Hearing loss in adults with Fabry disease treated with enzyme replacement therapy. J. Inherit. Metab. Dis. 38 (2015) 351–358. doi: 10.1007/s10545-014-9783-7.

[137] A Keilmann, S Hegemann, G Conti, D Hajioff, Fabry disease and the ear, in: A Mehta, M Beck, G Sunder-PLassmann (Eds), Fabry Disease: Perspectives from 5 years of FOS, Oxford PharmaGenesis, Oxford, 2006, Chapter 25.

[138] Sergi B, Conti G, Paludetti G, Interdisciplinary Study Group on Fabry Disease, Inner ear involvement in Anderson-Fabry disease: long-term follow-up during enzyme replacement therapy. Acta Otorhinolaryngol. Ital. 30 (2010) 87–93.

[139] Clinkard DJ, Amoodi H, Lin VY,Chen JM, Nedzelski JM, Improved hearing with cochlear implantation in Fabry's disease. Cochlear Implants Int. 12 (2011) 238–240. doi: 10.1179/1754762811Y0000000004.

[140] Pensabene L, Sestito S, Nicoletti A, Graziano F, Strisciuglio P, Concolino D, Gastrointestinal symptoms of patients with Fabry disease. Gastroenterol. Res. Pract. 2016 (2016) 9712831. doi: 10.1155/2016/9712831.

[141] Kulich KR, Madisch A, Pacini F, et al., Reliability and validity of the Gastrointestinal Symptom Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire in dyspepsia: a six-country study. Health Qual Life Outcomes. 6 (2008) 12. doi: 10.1186/1477-7525-6-12.

[142] Lewis SJ, Heaton KW, Stool form scale as a useful guide to intestinal transit time. Scand. J. Gastroenterol. 32 (1997) 920–924.

[143] Hoffmann B, Schwarz M, Mehta A, Keshav S; Fabry Outcome Survey European Investigators, Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin. Gastroenterol. Hepatol. 5 (2007) 1447–1453.

[144] Buda P, Wieteska-Klimczak A, Ksiazyk J, et al., Gastrointestinal phenotype of Fabry disease in a patient with pseudoobstruction syndrome. JIMD Rep. 4 (2012) 25–28. doi: 10.1007/8904_2011_63.

[145] Hyams JS, Davis P, Sylvester FA, Zeiter DK, Justinich CJ, Lerer T, Dyspepsia in children and adolescents: a prospective study. J. Pediatr. Gastroenterol. Nutr. 3- (2000) 413–418.

[146] Tielemans MM, Jaspers Focks J, van Rossum LG, et al., Gastrointestinal symptoms are still prevalent and negatively impact health-related quality of life: a large cross-sectional population based study in The Netherlands. PLoS One. 8 (2013) e69876. doi: 10.1371/journal.pone.0069876.

[147] Chitkara DK, Rawat DJ, Talley NJ, The epidemiology of childhood recurrent abdominal pain in Western countries: a systematic review. Am. J. Gastroenterol. 100 (2005) 1868–1875.

[148] Tokuda Y, Takahashi O, Ohde S, et al., Gastrointestinal symptoms in a Japanese population: a health diary study. World J. Gastroenterol. 13 (2007) 572–578.

[149] Buda P, Książyk J, Tylki-Szymanska A, Gastroenterological complications of Anderson-Fabry disease. Curr. Pharm. Des. 19 (2013) 6009–6013.

[150] Eliakim R, Video capsule endoscopy of the small bowel. Curr. Opin. Gastroenterol. 29 (2013) 133–139. doi: 10.1097/MOG.0b013e32835bdc03.

[151] Wilcox WR, Feldt-Rasmussen U, Martins AM, et al., Improvement of Fabry disease-related gastrointestinal symptoms in a significant proportion of female patients treated with agalsidase beta: data from the Fabry Registry. JIMD Rep. (2017). [Epub ahead of print]. doi: 10.1007/8904_2017_28.

[152] Watt T, Burlina AP, Cazzorla C, et al., Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. Genet. Med. 12 (2010) 703–712. doi: 10.1097/GIM.0b013e3181f13a4a.

[153] Hughes DA, Barba Romero MÁ, Hollak CE, et al., Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS--the Fabry Outcome Survey. Mol. Genet. Metab. 103 (2011) 207–214. doi: 10.1016/j.ymgme.2011.03.022

[154] Dehout F, Roland D, Treille de Granseigne S, et al., Relief of gastrointestinal symptoms under enzyme replacement therapy in patients with Fabry disease. J. Inherit. Metab. Dis. 27 (2004) 499–505. doi: 10.1023/B:BOLI.0000037342.59612.69

[155] Politei J, Thurberg BL, Wallace E, et al., Gastrointestinal involvement in Fabry disease. So important, yet often neglected. Clin. Genet. 89 (2016) 5–9. doi: 10.1111/cge.12673.

[156] Cable WJ, Kolodny EH, Adams RD, Fabry disease: impaired autonomic function. Neurology. 32 (1982) 498–502.

[157] Orteu CH, Jansen T, Lidove O, et al.; FOS Investigators, Fabry disease and the skin: data from FOS, the Fabry outcome survey. Br. J. Dermatol. 157 (2007) 331–337.

[158] Møller AT, Bach FW, Feldt-Rasmussen U, et al., Autonomic skin responses in females with Fabry disease. J. Peripher. Nerv. Syst. 14 (2009) 159–164. doi: 10.1111/j.1529-8027.2009.00227.x.

[159] Ellaway PH, Kuppuswamy A, Nicotra A, Mathias CJ, Sweat production and the sympathetic skin response: improving the clinical assessment of autonomic function. Auton. Neurosci. 155 (2010) 109–114. doi: 10.1016/j.autneu.2010.01.008

[160] Schiffmann R, Floeter MK, Dambrosia JM, et al., Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease. Muscle Nerve. 28 (2003) 703–710.

[161] Zampetti A, Orteu CH, Antuzzi D, et al.; Interdisciplinary Study Group on Fabry Disease (ISGF), Angiokeratoma: decision-making aid for the diagnosis of Fabry disease. Br. J. Dermatol. 166 (2012) 712–720. doi: 10.1111/j.1365-2133.2012.10742.x.

[162] C Orteu, Dermatological manifestations of Fabry Disease, in: D Elstein, G Altarescu, M Beck (Eds), Fabry Disease, Springer, New York, 2010, Chapter 14, pp. 259–274. doi: 10.1007/978-90-481-9033-1_14.

[163] Luna PC, Boggio P, Larralde M, Dermatologic Aspects of Fabry Disease. J. Inborn Errors Metab. Screen. 4 (2016) 1–7. Doi: 10.1177/2326409816661353.

[164] Orssaud C, Dufier JL, Germain DP, Ocular manifestations in Fabry disease: a survey of 32 hemizygous male patients. Ophthalmic Genet. 24 (2003) 129–139.

[165] Sivley MD, Wallace EL, Warnock DG, Benjamin WJ, Conjunctival lymphangiectasia associated with classic Fabry disease. Br. J. Ophthalmol. 102 (2018) 54–58. doi: 10.1136/bjophthalmol-2016-310088

[166] van der Tol L, Sminia ML, Hollak CE, Biegstraaten M, Cornea verticillata supports a diagnosis of Fabry disease in non-classical phenotypes: results from the Dutch cohort and a systematic review. Br. J. Ophthalmol. 100 (2016) 3–8. doi: 10.1136/bjophthalmol-2014-306433.

[167] Sodi A, Ioannidis AS, Mehta A, Davey C, Beck M, Pitz S, Ocular manifestations of Fabry's disease: data from the Fabry Outcome Survey. Br. J. Ophthalmol. 91 (2007) 210–214.

[168] Fledelius HC, Sandfeld L, Rasmussen ÅK, Madsen CV, Feldt-Rasmussen U, Ophthalmic experience over 10 years in an observational nationwide Danish cohort of Fabry patients with access to enzyme replacement. Acta Ophthalmol. 93 (2015) 258–264. doi: 10.1111/aos.12588.

[169] Mersebach H, Johansson JO, Rasmussen AK, et al., Osteopenia: a common aspect of Fabry disease. Predictors of bone mineral density. Genet. Med. 9 (2007) 812–818.

[170] Germain DP, Benistan K, Boutouyrie P, Mutschler C, Osteopenia and osteoporosis: previously unrecognized manifestations of Fabry disease. Clin. Genet. 68 (2005) 93–95.

[171] Talbot A, Ghali JR, Nicholls K, Antiepileptic medications increase osteoporosis risk in male Fabry patients: bone mineral density in an Australian cohort. JIMD Rep. 17 (2014) 29–36. doi: 10.1007/8904_2014_328.

[172] Drechsler C, Schmiedeke B, Niemann M, et al., Potential role of vitamin D deficiency on Fabry cardiomyopathy. J. Inherit. Metab. Dis. 37 (2014) 289–295. doi: 10.1007/s10545-013-9653-8.

[173] Magage S, Lubanda JC, Susa Z, et al., Natural history of the respiratory involvement in Anderson-Fabry disease. J. Inherit. Metab. Dis. 30 (2007) 790–799.

[174] Svensson CK, Feldt-Rasmussen U, Backer V, Fabry disease, respiratory symptoms and airway limitation – a systematic review. European Clin. Respir. J. 2 (2015). doi: 10.3402/ecrj.v2.26721.

[175] Wang RY, Abe JT, Cohen AH, Wilcox WR. Enzyme replacement therapy stabilizes obstructive pulmonary Fabry disease associated with respiratory globotriaosylceramide storage. J. Inherit. Metab. Dis. 31 Suppl 2 (2008) S369–S374. doi: 10.1007/s10545-008-0930-x.

[176] Kim W, Pyeritz RE, Bernhardt BA, Casey M, Litt HI, Pulmonary manifestations of Fabry disease and positive response to enzyme replacement therapy. Am. J. Med. Genet. A. 143 (2007) 377–381.

[177] Odler B, Cseh Á, Constantin T, et al., Long time enzyme replacement therapy stabilizes obstructive lung disease and alters peripheral immune cell subsets in Fabry patients. Clin. Respir. J. (2016) [Epub ahead of print]. doi: 10.1111/crj.12446.

[178] Arends M, Hollak CE, Biegstraaten M, Quality of life in patients with Fabry disease: a systematic review of the literature. Orphanet. J. Rare Dis. 10 (2015) 77. doi: 10.1186/s13023-015-0296-8.

[179] Concolino D, Degennaro E, Parini R; Fabry Delphi working group; Fabry Delphi working group, Delphi consensus on the current clinical and therapeutic knowledge on Anderson-Fabry disease. Eur. J. Intern. Med. 25 (2014) 751–756. doi: 10.1016/j.ejim.2014.07.009.

[180] Borgwardt L, Feldt-Rasmussen U, Rasmussen AK, Ballegaard M, Meldgaard Lund A, Fabry disease in children: agalsidase-beta enzyme replacement therapy. Clin. Genet. 83 (2013) 432–438. doi: 10.1111/j.1399-0004.2012.01947.x.

[181] Milligan A, Hughes D, Goodwin S, Richfield L, Mehta A, Intravenous enzyme replacement therapy: better in home or hospital? Br. J. Nurse. 15 (2006) 330–333. doi: 10.12968/bjon.2006.15.6.20681.

[182] Beck M, Gaedeke J, Martus P, Karabul N, Rolfs A, Home-based infusion therapy – a feasible approach for chronically ill patients? A new path to provide superior patient care exemplified in Fabry disease, Dtcsh. Med. Wochenschr. 138 (2013) 2345–2350 [German]. doi: 10.1055/s-0033-1349624.

[183] Hopkin RJ, Jefferies JL, Laney DA, et al., The management and treatment of children with Fabry disease: a United States-based perspective. Mol. Genet. Metab. 117 (2016) 104–113. doi: 10.1016/j.ymgme.2015.10.007

[184] Ortiz A, Germain DP, Desnick RJ, et al., Fabry disease revisited: Management and treatment recommendations for adult patients. Mol. Genet. Metab. 123 (2018) 417-427. doi: 10.1016/j.ymgme.2018.02.014

[185] Germain DP, Hughes DA, Nicholls K, et al., Treatment of Fabry's disease with the pharmacologic chaperone migalastat. N. Engl. J. Med. 375 (2016) 545–555. doi: 10.1056/NEJMoa1510198.

[186] Germain DP, Fan JQ, Pharmacological chaperone therapy by active-site-specific chaperones in Fabry disease: in vitro and preclinical studies. Int. J. Clin. Pharmacol. Ther. 47 (2009) S111–117.

[187] Germain DP, Giugliani R, Hughes D, et al., Safety and pharmacodynamic effects of a pharmacological chaperone on a-galactosidase A activity and globotriaosylceramide

clearance in Fabry disease: report from two phase 2 clinical studies. Orphanet J. Rare Dis. 7 (2012) 91. doi: 10.1186/1750-1172-7-91.

[188]   Warnock DG, Mauer M, Fabry disease: dose matters. J. Am. Soc. Nephrol. 25 (2014) 653–655. doi: 10.1681/ASN.2013121322.

[189]   Germain DP, Fabry disease: recent advances in enzyme replacement therapy. Expert Opin. Investig. Drugs 11 (2002) 1467–1476.

[190]   Lenders M, Stypmann J, Duning T, Schmitz B, Brand SM, Brand E, Serum-mediated inhibition of enzyme replacement therapy in Fabry disease. J. Am. Soc. Nephrol. 27 (2016) 256–264. doi: 10.1681/ASN.2014121226.

[191]   Lenders M, Schmitz B, Brand SM, Foell D, Brand E, Characterization of drug-neutralizing antibodies in patients with Fabry disease during infusion, J. Allergy Clin. Immunol. (2018 in press) doi: 10.1016/j.jaci.2017.12.1001

[192]   Bodensteiner D, Scott CR, Sims KB, Shepherd GM, Cintron RD, Germain DP, Successful reinstitution of agalsidase beta therapy in Fabry disease patients with previous IgE-antibody or skin-test reactivity to the recombinant enzyme. Genet. Med. 10 (2008) 353–358. doi: 10.1097/GIM.0b013e318170f868

[193]   Hughes DA, Nicholls K, Shankar SP, et al., Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J. Med. Genet. 54 (2017) 288–296. doi: 10.1136/jmedgenet-2016-104178.

[194]   Ashe KM, Budman E, Bangari DS, et al.; Efficacy of enzyme and substrate reduction therapy with a novel antagonist of glucosylceramide synthase for Fabry disease. Mol. Med. 21 (2015) 389–399. doi: 10.2119/molmed.2015.00088.

[195]   Del Pozo-Rodríguez A, Solinís MÁ, Rodríguez-Gascón A, Applications of lipid nanoparticles in gene therapy. Eur. J. Pharm. Biopharm. 109 (2016) 184–193. doi: 10.1016/j.ejpb.2016.10.016.