POLISH ARCHIVES OF
Internal Medicine
POLSKIE ARCHIWUM MEDYCYNY WEWNĘTRZNEJ

ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formated version will be made available soon.

Enzyme replacement therapy in Fabry disease in Poland – position statement

Authors: Michał Nowicki, Stanisława Bazan-Socha, Beata Błażejewska-Hyzorek, Ryszard Gellert, Jacek Imiela, Jarosław Kaźmierczak, Mariusz Kłopotowski, Zofia Oko-Sarnowska, Krzysztof Pawlaczyk, Piotr Ponikowski, Jarosław Sławek, Jolanta Sykut-Cegielska, Adam Witkowski, Danuta Zwolińska

Article type: Special report

Received: October 16, 2019.

Accepted: November 22, 2019.

Published online: December 20, 2019.

ISSN: 1897-9483

This is an Open Access article distributed under the terms of the Creative Commons Attribution- NonCommercial- ShareAlike 4.0 International License (CC BY- NC- SA4.0), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material, provided the original work is properly cited, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at pamw@mp.pl.

Enzyme replacement therapy in Fabry disease in Poland - position statement.

short title: **ERT in Fabry disease in Poland**

Michał Nowicki[1*], Stanisława Bazan-Socha[2], Beata Błażejewska-Hyzorek[3], Ryszard Gellert[4], Jacek Imiela[5], Jarosław Kaźmierczak[6], Mariusz Kłopotowski[7], Zofia Oko-Sarnowska[8], Krzysztof Pawlaczyk[9], Piotr Ponikowski[10,11], Jarosław Sławek[12,13], Jolanta Sykut-Cegielska[14], Adam Witkowski[7], Danuta Zwolińska[15]

1 Department of Nephrology, Hypertension, and Kidney Transplantation, Medical University, Lodz, Poland

2 Department of Internal Medicine, Jagiellonian University Medical College, Cracow, Poland

3 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

4 Department of Nephrology and Internal Medicine, Centre of Postgraduate Medical Education, Warsaw, Poland

5 Department of Internal Medicine and Nephrology, Miedzyleski Hospital, Warsaw, Poland.

6 Department of Cardiology, Pomeranian Medical University, Szczecin, Poland

7 Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland

8 1st Department of Cardiology, Poznan University of Medical Science, Poznan, Poland

9 Department of Nephrology, Transplantology, and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland

10 Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland

11 Cardiology Department, Centre for Heart Disease, Military Hospital, Wroclaw, Poland

12 Department of Neurological-Psychiatric Nursing, Medical University of Gdansk, Gdansk, Poland,

13 Neurology Department, St Adalbert Hospital Copernicus, Gdansk, Poland

14 Department of Inborn Errors of Metabolism and Pediatrics, Institute of Mother and Child, Warsaw, Poland

15 Department of Pediatric Nephrology, Wroclaw Medical University, Poland.

Corresponding author:

*Corresponding author: nefro@wp.pl; Pomorska 251 street, 92-213 Łódź

phone: +48 42 201 44 00; fax: + 48 42 201 44 01

Conflict of interest:

R.G., J.K., P.P., A.W., D.Z. report consultation fees for Sanofi Genzyme; M.N., Z.O-S., K.P., J.S. report consultation/speakers fees for Sanofi Genzyme; S.B-S., B.B-H., M.K. report consultation fees/speakers fees for Sanofi Genzyme and Shire. J.I., J.S-C. report no conflict of interest.

Introduction

Fabry disease (OMIM #301500) is a rare, inherited, lysosomal, genetic storage disease caused by mutations in the *GLA* gene on the X chromosome, which results in a lack or significant deficiency of the lysosomal enzyme α-galactosidase A (α-GAL A). This deficiency leads to the accumulation of glycosphingolipids (mainly globotriaosylceramide [GL-3] and its deacylated form globotriaosylsphingosine [lyso-GL-3]) in many cells of the body, and to the development of multisystem complications that impair the quality of life and lead to premature death (Table 1) [1].

The clinical picture of Fabry disease is very diverse and depends on the α-GAL A activity. A complete lack of or trace α-GAL A activity (<5%) causes the classic form of the disease, which mainly affects male patients. People with partially preserved enzymatic activity develop the nonclassical late-onset form of Fabry disease. The onset and severity of symptoms in women are primarily dependent on the random pattern of inactivation of one of the two X chromosomes [2, 3].

The first symptom of the classic form of the disease, already seen in early childhood, is chronic or paroxysmal neuropathic pain in the hands and feet, defined as acroparesthesia. Later, other symptoms associated with thin nerve fiber involvement occur, such as impaired perspiration (hypohidrosis, anhidrosis), abdominal pain, and diarrhea. Characteristic symptoms of the classic form also include angiokeratoma-type cutaneous lesions and corneal opacities (cornea verticillata) [1]. Even in childhood, clinically silent proteinuric chronic kidney disease may occur with microalbuminuria or glomerulosclerosis. Multiorgan symptoms of the classic form of Fabry disease usually appear in young adults and may include chronic kidney disease, left ventricular hypertrophy, myocardial fibrosis, arrhythmias and conduction abnormalities, transient ischemic attacks, and strokes. People with late-onset Fabry disease typically have cardiac symptoms, a stroke, or chronic kidney disease in the

fourth or fifth decade of life [1]. The classic form of Fabry disease is an early-onset multisystem disease that typically presents with cornea verticillata and angiokeratomas. In contrast, the non-classic form has a later onset and usually affects a single organ, most often the heart; angiokeratomas or cornea verticillata are usually not found.

The intensity of cell and organ changes progresses in the course of Fabry disease. Metabolite accumulation begins as early as in the fetal period, leading to the involvement of many tissues and severe organ dysfunction (Fig. 1) [4]. The life expectancy of men with Fabry disease is shorter by 15–20 years, and that of women by 6–10 years, in relation to the average life expectancy in the population [5]. It should be emphasized that even in the stage of late complications, the diagnosis of Fabry disease is difficult. Chronic kidney disease, and cardiac and neurological symptoms are very common in the general population and are usually caused by common civilization diseases.

The estimated prevalence of Fabry disease in the general world population is 1/100,000. The prevalence of Fabry disease reported in Polish studies is 2.5/100,000 in the entire population: 1/40,000 in men and 0.85/100,000 (1/117,000) in women [6-8]. In men, the prevalence of the classic mutations, which result in no detectable α-GAL A activity, is about 1 in 20,000 to 45,000. The prevalence of the non-classic mutations, with some α-GAL A activity, is about 10 times greater. In women, the prevalence of mutations is higher than in men (2:1 ratio) because Fabry disease is inherited with the X chromosome.

In Poland, there have been no guidelines for the diagnosis and management of Fabry's disease [9]. The position statement was prepared by an interdisciplinary group of experts and approved by the Boards of the Polish Cardiac Society, the Polish Society of Inborn Errors of Metabolism, the Polish Society of Internal Medicine, the Polish Society of Nephrology, and the Polish Society of Neurology. Although disease-specific treatments for Fabry disease include other treatments than ERT (e.g. migalast), only ERT is currently reimbursed in

Poland. This position paper aims to provide practical recommendations for physicians who treat patients with Fabry disease in Poland and therefore it concentrates on ERT.

Diagnosis of Fabry disease

Due to the lack of specific symptoms indicative of Fabry disease, the diagnostic process is difficult and can last for many years. The diagnosis of Fabry disease requires the simultaneous consideration of the clinical picture and the results of enzymatic, biochemical, and genetic tests [10, 11]. Most of the symptoms of Fabry disease, including hypertrophic cardiomyopathy, proteinuric chronic kidney disease, and ischemic stroke, are nonspecific and have a wide differential diagnosis. The identification of certain symptoms such as cornea verticillata in a slit lamp or the histopathological confirmation of angiokeratoma is of greater diagnostic significance [10, 11].

To diagnose the disease, α-GAL A activity is measured in whole blood (dried blood spot method), plasma, or leukocytes. An activity of <5%, usually found in men with the classic form of the disease or in homozygous women, definitely indicates Fabry disease. Testing for α-Gal A activity alone is diagnostic in men only. In women, α-Gal A activity may be normal or only slightly decreased; therefore, a disease-causing mutation in the GLA gene must be found to diagnose the disease. Genetic testing should be offered to men as well to determine disease form, enable family screening, and rule our benign polymorphisms associated with reduced α-Gal A activity (Table 2) [11]. Additional diagnostic information to assess the pathogenicity of mutations (variants of unknown significance) and disease severity (in heterozygous women) can be obtained by the determination of the disease biomarkers (especially plasma lyso-GL-3). Detection of GL-3 deposits in histopathological examination (of heart, kidneys, skin) indicates Fabry disease, but should be interpreted together with clinical, biochemical, and genetic data.

Renal complications

Chronic kidney disease is a serious and frequent complication of Fabry disease. In the asymptomatic period, histopathological examination may indicate the accumulation of glycosphingolipids in kidney cells, including podocytes and cells of the endothelium, mesangium, and renal tubules. Deposits of glycosphingolipids in the kidneys are present as early as in the fetal period [12, 13]. Further progression of the disease leads to interstitial fibrosis, glomerulosclerosis, and renal tubular atrophy. These changes cause albuminuria and proteinuria and progressive reduction of glomerular filtration followed by renal failure until end-stage, requiring dialysis or renal transplantation [11].

The stage of chronic kidney disease in Fabry disease should be assessed based on the glomerular filtration rate (GFR) and the severity of albuminuria/proteinuria. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is recommended to estimate glomerular filtration [14]. In children, GFR should be determined with nuclear techniques before deciding on treatment. A kidney biopsy may help in the case of diagnostic doubts and in the evaluation of the effectiveness of enzyme replacement therapy. The assessment and treatment of chronic kidney disease in adult patients with Fabry disease should follow the general KDIGO 2012 recommendations [14].

Cardiac complications

Cardiac complications of Fabry disease are frequent, affect about 40–60% of patients, both men and women, and are a significant cause of premature mortality [15-20]. The accumulation of glycosphingolipids in cardiomyocytes, ischemic lesions associated with the involvement of small vessels, and inflammation contribute to the concentric hypertrophy of the left ventricle and subsequent fibrosis. Hypertrophy of the left ventricle, observed in about

50% of men and 30% of women, is most often diagnosed from the third decade of life [16]. With the progression of the disease, irreversible changes occur, including fibrosis [21].

Cardiac hypertrophy can be assessed with an electrocardiogram (ECG), echocardiography, and magnetic resonance imaging (MRI) of the heart, and myocardial fibrosis of the left ventricle can be assessed by late gadolinium enhancement (LGE) in MRI. The earliest cardiac manifestation of Fabry disease is the initial shortening, followed by the prolongation of the PR interval, bradycardia, progressive atrioventricular and intraventricular conduction disorders, and cardiac hypertrophy. Many patients develop chronic heart failure, with a preserved ejection fraction that decreases with the progression of the disease. Angina is frequently reported in patients with Fabry disease. Usually epicardial coronary arteries are normal, but perfusion defects and slow coronary flow can be found on angiography and on myocardial perfusion tomography. Endomyocardial biopsy shows lumen narrowing of intramyocardial arteries due to hypertrophy and hyperplasia of smooth muscle and endothelial cells, and increased fibrosis of the intimal and medial layer [22] and changes in the morphology of the heart valves resulting in regurgitation are also frequent complications of Fabry disease [22, 23]. In addition, myocardial fibrosis increases the risk of life-threatening arrhythmias. The use of cardiac magnetic resonance native T1 mapping allows assessment of myocardial involvement before left ventricle hypertrophy. The incidence of clinically significant ventricular arrhythmias is low, but there is relatively high incidence of bradycardia and need for pacing [24]. It is suspected that sudden cardiac death in Fabry disease is related to bradycardia [24].

After the diagnosis of Fabry disease, 24–48-hour Holter ECG monitoring is recommended [24]. Early detection of cardiac arrhythmias and conduction disorders allows for the introduction of appropriate treatment in some cases, such as cardiac pacing or cardioverter-

defibrillator implantation, or antithrombotic treatment in atrial fibrillation. Some forms of arrhythmias may also be treated with radiofrequency ablation.

Neurological complications

Fabry disease can affect both the peripheral and central nervous systems. The cause of injury in the peripheral nervous system is the accumulation of GL-3 deposits in the ganglia of the dorsal roots of the spinal cord. Along with small fiber neuropathy it may clinically present as severe neuropathic pain in hands and feet, both chronic and paroxysmal (pain crises). This is one of the first symptoms of the disease (red flag!), although it does not occur in all patients. Involvement of autonomic fibers by the disease may result in secretory problems (perspiration, salivation, and secretion of tears), high temperature hypersensitivity, abdominal pain, hypotonia, and reduced exercise tolerability [25-27]. The diagnosis of neuropathy is usually hampered by correct electroneurography results. More advanced tests, not performed routinely (not available in the majority of neurophysiological labs), are required, i.e. skin biopsy or laser-evoked potentials.

The mechanisms involved in injury to the central nervous system are not well understood, but changes in cerebral vessels and cardiac embolism are thought to contribute to ischemic changes in the brain [28]. Fabry disease increases the risk of ischemic stroke (4.2-fold in the population of stroke patients aged 35–45 years), which usually occurs before the age of 50 years. [29]. Stroke can be both ischemic and hemorrhagic. Ischemic stroke is most often found in the vertebrobasilar region; the “pulvinar” sign (hyperintense signal in the T1 MRI sequence) and enlargement of the basilar artery are sometimes observed. The distribution of ischemic lesions (white matter hyperintensities associated with small vessel disease) may be

similar to those seen in multiple sclerosis or hypertensive encephalopathy [30]. Involvement of large vessels is usually secondary to heart disease (cardiogenic strokes). Early-onset stroke in the absence of other causes, as well as co-existing renal and cardiac disease with burning pains in the feet and hands in anamnesis, should lead to the diagnostic procedures for Fabry disease. Fabry disease is also associated with neuropsychiatric problems like depression and cognitive decline; therefore, antidepressants may be helpful as symptomatic therapy. [31]

High-risk populations

Published studies and guidelines indicate the need to perform diagnostic testing for Fabry disease in patients with illnesses or symptoms that are classic and frequent complications of this disease (Table 3) [28, 32-36].

Family screening and genetic counseling

When a diagnosis of Fabry disease has been made, it is crucial to do a clinical and genetic screening of the patient's family members. Typically, such screening reveals Fabry disease in several family members, who can benefit from early diagnosis and treatment. The diagnosis of Fabry disease causes much distress and raises many questions among patients and their families. Thus, genetic counseling provided by a geneticist with expertise in Fabry disease must be offered to explain the X-linked pattern of inheritance and the available diagnostic and management options. Apart from the information on the medical aspects of the disease, patients should receive psychological support when needed. Information on the methods of prenatal diagnosis should be given to patients who plan to have children [11]

Enzyme replacement therapy in Fabry disease

International standards and guidelines unequivocally accept the use of enzyme replacement therapy (ERT) as an optimal and specific treatment method for patients with confirmed Fabry disease, which stops the progression of organ changes and stabilizes or improves organ

function (Table 4) [11, 37]. Studies have confirmed the beneficial effect of ERT on both the removal of GL-3 deposits from organs and the severity of the disease on biochemical evaluation (GL-3, lyso-GL-3 in plasma). The effect on intermediate endpoints, including albuminuria or proteinuria, estimated glomerular filtration rate, the mass of the left ventricle, and the severity of pain, has also been confirmed [38, 39]. In addition, ERT (agalsidase beta) led to significant reductions in the clinically significant composite renal/cardiac/neurological endpoint (-61%, p=0.034, for the "per-protocol" population) [40, 41].

Numerous clinical observations also indicate the dependence of the clinical effects on the stage of the disease in which ERT was initiated. The use of ERT in patients at a younger age, with less severe organ changes, without irreversible complications, or without previous serious cardiovascular events, resulted in more beneficial clinical effects [40, 42-46].

Currently, two human α-GAL A isoforms are available in therapy: agalsidase alfa (Replagal, Shire, EMA registration in 2001) and agalsidase beta (Fabrazyme, Sanofi Genzyme, EMA registration in 2001, FDA registration in 2003). Both drugs are administered every two weeks by intravenous infusion: agalsidase alfa at a dose of 0.2 mg /kg bw, and agalsidase beta at a dose of 1.0 mg/kg bw [47, 48]. There have been no direct comparative studies assessing the long-term impact of these therapies on significant clinical parameters in a sufficiently large group of patients with a homogeneous phenotype. However, available observations indicate a relationship between the therapeutic effect and the dose of ERT (nine-fold higher intracellular concentration of agalsidase beta as compared to agalsidase alfa). This dependence is confirmed by the results of comparative assessments and studies in which agalsidase alfa was switched to agalsidase beta or vice versa [49-52].

The most commonly reported adverse reactions associated with ERT were post-infusion reactions (more frequent with agalsidase beta). Most of the reactions were mild to moderate, were not a reason for discontinuation of therapy, and subsided with subsequent

administrations. To minimize their severity, it is possible to reduce the rate of ERT administration and give pre-medication with antihistamines, analgesics, and/or corticosteroids. ERT cannot be used simultaneously with chloroquine, amiodarone, benzoquinone, or gentamycin because these substances potentially inhibit the activity of intracellular α-GAL A [47,48].

Since 2016, the oral drug migalastat (Galafold, Amicus) has also been registered for use in the treatment of Fabry disease. Migalastat is a pharmacological chaperone that works by stabilizing the mutated forms of α-GAL A and increasing their availability in lysosomes. Migalastat is indicated for the treatment of adults and adolescents from 16 years of age, but only in patients with a mutation that makes them sensitive to its action [53].

Indications for starting and stopping enzyme replacement therapy and contraindications

As already mentioned, early enzyme replacement is crucial to suppress the progression of Fabry disease. According to the European guidelines for the management of Fabry disease published in 2018, ERT should be initiated in all men with the classic form of the disease, regardless of symptoms, and in symptomatic women with the classic form. ERT should also be initiated in women who have positive laboratory tests, histological, or imaging studies indicating injury to kidneys, heart, or central nervous system. Regarding the non-classical form and a form in which variants of unknown significance (VUS) are found, ERT is indicated in the presence of symptoms or when there is injury to kidneys, heart, or central nervous system attributable to Fabry disease, which may require a histological or biochemical confirmation [11]. Moreover, in patients with VUS, a geneticist with expertise in Fabry disease should give advice on the pathogenicity of a given VUS.

In the opinion of the authors of this position statement, in the context of Polish clinical practice, appropriate look at the indications for starting ERT was presented in the Canadian Fabry Initiative Group guidelines published in 2017 [52]; they are the basis for the clinical recommendations for starting and stopping ERT, as well as its contraindications, presented in Table 5.

Symptomatic treatment

In addition to ERT, people with Fabry disease should receive symptomatic treatment tailored to their individual needs in accordance with relevant current clinical recommendations. It is important to screen for modifiable risk factors such as diabetes, hypertension, arrhythmia, hyperlipidemia, smoking, sedentary lifestyle, depression, microalbuminuria, and renal failure. Early detection of risk factors allows them to be controlled and reduces the overall risk of complications. Cardiovascular risk can be reduced by modifying the lifestyle and treating hypertension, hyperlipidemia, and heart failure. Heart arrhythmias may require implantation of a cardioverter-defibrillator as part of the prevention of sudden cardiac death. In addition, patients with Fabry disease, regardless of gender and age, should receive anticoagulant therapy for the prophylaxis of arterial emboli in case of atrial fibrillation. Treatment of heart failure and chronic kidney disease should be carried out according to general recommendations. Treatment of painful neuropathy requires the use of gabapentinoids (gabapentin, pregabalin). Carbamazepine is also recommended, as are venlafaxine or duloxetine in the case of coexisting neuropathic pain and depression [4,10,11].

Contribution statement: All of the authors were involved in manuscript preparation and the final version was edited and approved by all of them.

References:

1. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010; 5: 30.
2. Echevarria L, Benistan K, Toussaint A, et al. X-chromosome inactivation in female patients with Fabry disease. Clin Genet. 2016; 89(1): 44-54.
3. Wilcox WR, Oliveira JP, Hopkin RJ, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab. 2008; 93(2): 112-128.
4. Wanner C. Fabry disease model: a rational approach to the management of Fabry disease. Clin Ther. 2007; 29 Suppl A: S2-5.
5. Schiffmann R. Fabry disease. Handb Clin Neurol. 2015; 132: 231-248.
6. Tuttolomondo A, Pecoraro R, Simonetta I, et al. Anderson-Fabry disease: a multiorgan disease. Curr Pharm Des. 2013; 19: 5974-5996.
7. Bodzioch M, Bodzioch K. Fabry disease. Med Prakt Neurol. 2014; 5: 55-61.
8. Zysk R, Nowak S. Association of Families with Fabry disease. The situation of patients with Fabry disease in Poland. Health Economics Consulting PEX Pharma Sequence. Warsaw 2018.
9. Bazan- Socha S, Kuczia P, Musiał J, Błażejewska- Hyżorek B. Fabry disease in Poland. Pol Arch Intern Med. 2018; 128: 567-568.
10. Sirrs S, Bichet DG, Iwanochko RM, et al. Canadian Fabry disease treatment guidelines 2017. Toronto: The Garrod Association; 2017 Sep 22. Dostępne z: http://www.garrod.ca/wp-content/uploads/Canadian-FD-Treatment-Guidelines-2017.pdf.
11. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Gen Metabol. 2018; 123: 416-427.
12. Tøndel C, Bostad L, Hirth A, et al. Renal biopsy findings in children and adolescents

with Fabry disease and minimal albuminuria. Am J Kidney Dis. 2008; 51(5): 767-776.

13. Tøndel C, Bostad L, Larsen KK, et al. Agalsidase benefits renal histology in young patients with Fabry disease. J Am Soc Nephrol. 2013; 24: 137-148.
14. KDIGO 2012. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2012; 3: 1-150.
15. Kampmann C, Baehner F, Whybra C, et al. Cardiac manifestations of Anderson-Fabry disease in heterozygous females. J Am Coll Cardiol 2002; 40(9): 1668-1674.
16. Kampmann C, Linhart A, Baehner F, et al. Onset and progression of the Anderson-Fabry disease related cardiomyopathy. Int J Cardiol. 2008; 130(3): 367-373.
17. Senechal M, Germain DP. Fabry disease: a functional and anatomical study of cardiac manifestations in 20 hemizygous male patients. Clin Genet. 2003; 63(1): 46-52.
18. Shah JS, Hughes DA, Sachdev B, et al. Prevalence and clinical significance of cardiac arrhythmia in Anderson-Fabry disease. Am J Cardiol. 2005; 96(6): 842-846.
19. 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. 2011; 57(9): 1093-1099.
20. Waldek S, Patel MR, Banikazemi M, et al. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med. 2009; 11(11): 790-796.
21. Weidemann F, Sanchez-Nino MD, Politei J, et al. Fibrosis: a key feature of Fabry disease with potential therapeutic implications. Orphanet J Rare Dis. 2013; 8: 116.
22. Chimenti C, Morgante E, Tanzilli G, et al. Angina in Fabry disease reflects coronary small vessel disease. Circ Heart Fail. 2008; 1: 161-169.
23. Morrissey RP, Philip KJ, Schwarz ER. Cardiac abnormalities in Anderson-Fabry disease and Fabry's cardiomyopathy. Cardiovasc J Afr. 2011; 22: 38-44.

24. Acharya D, Robertson P, Kay GN, et al. Arrhythmias in Fabry cardiomyopathy. Clin Cardiol. 2012; 35: 738-740.
25. Dötsch M, Marthol H, Stemper B, et al. Small fiber dysfunction predominates in Fabry neuropathy. J Clin Neurophysiol. 2002; 19: 575-586.
26. Uceyler N, Kahn AK, Kramer D, et al. Impaired small fiber conduction in patients with Fabry disease: a neurophysiological case-control study. BMC Neurol. 2013; 13: 47.
27. 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. 2011; 11: 61.
28. Kolodny E, Fellgiebel A, Hilz MJ, et al. Cerebrovascular Involvement in Fabry Disease: current status of knowledge. Stroke. 2015; 46: 302-313.
29. Sims K, Politei J, Banikazemi M, et al. Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry. Stroke. 2009; 40: 788-794.
30. Bolsover FE, Murphy E, Cipolotti L, et al. Cognitive dysfunction and depression in Fabry disease: a systematic review. J Inherit Metab Dis. 2014; 37: 177-187.
31. Cole AL, Lee PJ, Hughes DA, et al. Depression in adults with Fabry disease: a common and underdiagnosed problem. J Inherit Metab Dis. 2007; 30: 943-951.
32. Terryn W, Cocchat P, Froissart R et al. Fabry nephropathy: indications for screening and guidance for diagnosis and treatment by the European Renal Best Practice. Nephrol Dial Transplant. 2013 Mar;28(3):505-517
33. 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. 2014; 35(39): 2733-2779.

34. van der Tol L, Smid BE, Poorthuis BJ, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet. 2014; 51(1): 1-9.
35. Tanislav C, Kaps M, Rolfs A, et al. Frequency of Fabry disease in patients with small-fibre neuropathy of unknown aetiology: a pilot study. Eur J Neurol. 2011; 18: 631-636.
36. Laney DA, Fernhoff PM. Diagnosis of Fabry disease via analysis of family history. J Genet Couns. 2008; 17: 79-83.
37. Wanner C, Arad M, Baron R, et al. European expert consensus statement on therapeutic goals in Fabry disease. Mol Genet Metab. 2018; 124: 189-203.
38. 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. Mol Genet Metab. 2019; 126(3): 224-235.
39. 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. Mol Genet Metab Rep. 2019 (19):100454. doi: 10.1016/j.ymgmr.2019.100454.
40. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med. 2007; 146: 77-86.
41. El Dib R, Gomaa H, Ortiz A, et al. 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. 2017; 12: e0173358.
42. Germain DP, Charrow J, Desnick RJ, et al. Ten-year outcome of enzyme replacement

therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015; 52: 353-358.

43. Hopkin RJ, Cabrera G, Charrow J, et al. Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: Data from the Fabry Registry. Mol Genet Metab. 2016; 119: 151-159.
44. Weidemann F, Niemann M, Breunig F, et al. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation. 2009; 119: 524-529.
45. 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. 2016; 53: 495-502.
46. Fellgiebel A, Gartenschläger M, Wildberger K, et al. Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease. Cerebrovascular Dis. 2014; 38(6): 448-456.
47. Replagal – Characteristics of the Medicinal Product.
48. Fabrazyme – Characteristics of the Medicinal Product.
49. Arends M, Biegstraaten M, Wanner C, et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study. J Med Genet. 2018; 55: 351-358.
50. Skrunes R, Tøndel C, Leh S, et al. Long-Term Dose-Dependent Agalsidase Effects on Kidney Histology in Fabry Disease. Clin J Am Soc Nephrol. 2017; 12: 1470-1479.
51. Kramer J, Lenders M, Canaan-Kühl S, et al. Fabry disease under enzyme replacement therapy-new insights in efficacy of different dosages. Nephrol Dial Transplant. 2018; 33: 1362-1372.

52. Weideman F, Krämer J, Duning T, et al. Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch. J Am Soc Nephrol. 2014; 25: 837-849.

53. Galafold - Characteristics of the Medicinal Product

Tables:

Table 1. The most common renal, cardiac, neurological, and other complications associated with Fabry disease (based on Ortiz A et al., 2018) [11]

Renal complications	Cardiac complications	Neurological complications	Other complications
Pathological albuminuria/proteinuria Reduced glomerular filtration rate. Chronic kidney disease leading to insufficiency. Hypertension Premature death	Left ventricular hypertrophy. Heart arrhythmia (ventricular arrhythmia, atrial fibrillation, bradycardia). Myocardial fibrosis. Ischemia, myocardial infarction. Valve defects (mitral, aortic regurgitation). Reduced exercise tolerance. Heart failure. Premature death.	Neuropathic pain (chronic, pain crises). Stroke, transient ischemic attack White matter lesions in the brain Hearing loss Depression Autonomic system disorders: - gastrointestinal disorders (diarrhea, nausea, postprandial pain); - sweating disorders; Premature death.	Angiokeratoma-type skin lesions Cornea verticillata, retinal/conjunctival vascular changes. Cataract Dyspnea, dry cough, sleep breathing disorders. Moderate facial dysmorphia. Osteopenia, osteoporosis. Lymphoedema.

Table 2. Diagnostic confirmation of Fabry disease.

Male	Female
• determination of α-GAL A activity (no / significant deficiency) in the dry blood spot (DBS) test, plasma or peripheral blood leukocytes	• determination of lyso-GL-3 plasma levels in the dry blood spot (DBS) test (plasma α-GAL A activity is usually within the normal range)
• genetic testing for the presence of a pathogenic mutation	
• determination of the type of mutation to confirm the phenotype of the disease, exclusion of benign polymorphisms, or the need for family screening (For variant of uncertain significance (VUS), determination of pathogenicity based on clinical, biochemical or histopathological parameters and family history)	

Table 3. Populations of patients with special indications for diagnostic testing for Fabry disease

Indications for diagnostic testing for Fabry disease
• chronic kidney disease, proteinuria, or albuminuria of unknown origin • unexplained left ventricular hypertrophic cardiomyopathy • transient ischemic attacks/stroke in young people • white matter lesions with an unclear cause • unexplained neuropathy of thin nerve fibers • angiokeratoma or cornea verticillata • active family screening of patients with diagnosed Fabry disease (inheritance related to the X chromosome)

Table 4. Effect of enzyme replacement therapy on clinical parameters in patients with Fabry disease (based on Germain DP et al., 2019 (A); Germain DP et al., 2019 (B); Banikazemi M et al., 2007; El Dib R et al., 2017) [38-41]

Effect of enzyme replacement therapy on clinical parameters in patients with Fabry disease
• elimination of GL-3 deposits in kidney, heart, nerve cells, vascular endothelial cells • reduction of disease severity in biochemical evaluation (plasma GL-3, lyso-GL-3, urinary GL-3) • stabilization/limited progression/improvement of albuminuria and proteinuria • stabilization/limited progression of renal function (eGFR) • limited progression of left ventricular mass increase (LVM/LVMI, LVWT reduction) • improvement in the ECG assessment of conduction disorders • improvement of sweat function and PNS nerve sensitivity • reduction of neuropathic pain • limited progression of white matter lesions in the brain • reduction of clinically significant renal, cardiac, and neurological endpoints (agalsidase beta) • improvement in quality of life

Abbreviations: eGFR: estimated glomerular filtration rate; GL-3: globotriaosylceramide; lyso-GL-3: globotriaosylsphingosine; LVM: left ventricular mass; LVMI: left ventricular mass index; LVWT: left ventricular wall thickness, PNS: peripheral nervous system

Table 5. Indications for starting, contraindications, and indications for discontinuation of ERT in Fabry disease (modified by the authors based on the guidelines of the Canadian Fabry Initiative Group, Sirrs S et al., 2017) [10]

Indications for enzyme replacement therapy
Nephrological—one main criterion required or two minor ones
Main criteria: • Fabry nephropathy with reduced GFR * • persistent proteinuria ≥500 mg/day/1.73 m^2 after excluding other causes • high-risk pathology in kidney biopsy (glomerular sclerosis, tubular atrophy, vascular fibrosis or sclerosis)—only men Minor criteria: • hyperfiltration • isolated proteinuria 300 mg/day/1.73 m^2 or higher than the norm for age and sex and persisting for at least one year, after excluding other causes • renal tubular dysfunction • hypertension lasting at least one year • high-risk pathology in kidney biopsy (glomerulosclerosis, tubular atrophy, vascular fibrosis, or sclerosis) if there are indications for it—only women
Cardiac—2 criteria required
• left ventricular wall thickness >12 mm in men and >11 mm in women • left ventricular mass index in 2D echo assessment 20% above the norm for age • left ventricular mass increase by at least 5 g/m^2/year, with three measurements for a minimum of one year

- left ventricular diastolic dysfunction in the 2D + Doppler echocardiography (grade 2 or 3 according to the guidelines of the American Society of Echocardiography and/or the presence of abnormalities in the tracking of acoustic markers)
- loss of left ventricular base-to-apex circumferential strain gradient
- increased size of the left atrium in the 2D echo assessment; parasternal long-axis (PLAX) view of the left ventricle >40 mm; left atrial volume index >34 ml/m^2
- arrhythmia and conduction disorders: atrioventricular (AV) block, PR interval shortening, left bundle branch block, ventricular or atrial tachyarrhythmia, sinus bradycardia (without the use of drugs with negative chronotropic activity), or other causes
- moderate to severe regurgitation of the main or mitral valve
- late gadolinium enhancement (LGE) of left ventricular myocardium in cardiac MRI
- increase of N-terminal pro-brain natriuretic peptide (NT-proBNP) above the upper limit of the norm for age and sex or increase of high-sensitivity troponin (a replacement indicator of fibrosis) by more than twice the upper limit of normal

Neurological—1 criterion required

- previous stroke or transient ischemic attack (TIA)
- severe neuropathic pain that is resistant to treatment
- sudden one-sided hearing loss when other possible causes have been excluded
- acute ischemic optic neuropathy when other possible causes have been excluded

Symptoms involving the digestive system

- significant gastrointestinal symptoms not responding to other treatments for at least 6 months or associated with delayed growth or significant reduction in the quality of life

Contraindications for enzyme replacement therapy
• pregnancy (relative contraindication) and lactation • serious co-morbidities, with an estimated life expectancy below 1 year • severe cognitive impairment, regardless of the cause • serious complications in which the use of ERT will not significantly improve the quality of life • other diseases in which the benefit-risk ratio of using ERT is unfavorable
Discontinuation of enzyme replacement therapy
• insufficient patient compliance • patient's request • no clinical response to treatment after a reasonable (min. 1 year) period of observation • estimated life expectancy of less than one year due to serious co-morbidities or severe Fabry disease with end-stage heart failure if the patient is not a candidate for heart transplantation • permanent, serious neurocognitive impairment • serious, life-threatening infusion-related adverse reactions, despite prophylactic treatment

* For GFR <60 ml/min/1.73m^2, chronic kidney disease (CKD) grades 3-5: at least 2 concordant estimates or GFR measurements for a minimum of 3 months

For GFR 60–90 ml/min/1.73 m^2, CKD grade 2: at least 3 concordant estimates or GFR measurements for at least 6 months with a slope of the GFR curve greater than the age-related norm

For GFR>135 ml/min /1.73 m^2: a 15% decrease in GFR or a GFR curve slope greater than the age-related norm measured by nuclear medicine techniques. The estimated GFR is not precise in this respect and therefore cannot be used.

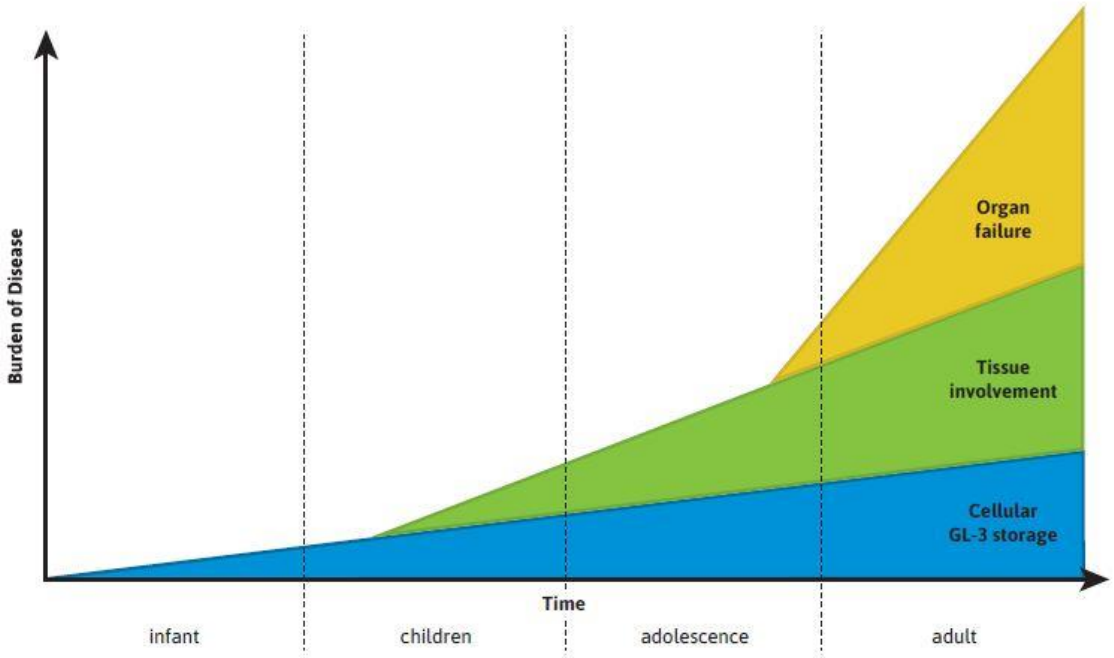

Fig. 1. The progression of Fabry disease. Modified from Clin Ther. Vol. 29 Suppl A, Wanner C, Fabry disease model: a rational approach to the management of Fabry disease: S2-5. © 2007 Excerpta Medica, Inc, with permission from Elsevier Inc. (Re-use must be cleared with Elsevier Inc.) [4]