Review Article on Current Management Aspects in Adult Congenital Heart Disease (ACHD): Part III

Contemporary therapeutics and new drug developments for treatment of Fabry disease: a narrative review

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Abstract: Fabry disease (OMIM 301500) is an X-linked (Xq22.1) lysosomal storage disorder leading to a progressive multisystem disease with high variability in both genotype and phenotype expression. The pathophysiological origin is found in an enzyme deficiency of the α-galactosidase A (enzyme commission no. 3.2.1.22) leading to accumulation of globotriaosylceramides in all lysosome carrying tissue. Especially organ manifestations of the heart, kidneys and nervous system are of significant prognostic value and might complicate with Fabry-associated pain, young aged cryptogenic stroke, proteinuria, kidney failure, hypertrophic cardiomyopathy, heart failure, malign cardiac rhythm disturbances and eventually sudden cardiac death. Up to the introduction of the first enzyme replacement agent in 2001, patients faced the disease's natural course with no disease-specific therapies available. Today, two recombinant enzyme replacement agents (Fabrazyme®, Sanofi Genzyme, Cambridge, MA, USA; Replagal®, Takeda Pharmaceutical, Tokio, Japan) and one oral chaperone therapy (Migalastat®, Amicus Therapeutics, USA) are available and well-established in daily clinical practice. Substrate reduction therapy, second-generation enzyme replacement agents and different gene therapy approaches are currently undergoing preclinical and clinical trial phases and aim to improve therapeutic success and long-term outcome of patients with Fabry disease. This narrative review summarizes the currently available therapeutic options and future perspectives in Fabry disease.

Keywords: Fabry disease; enzyme replacement therapy; chaperone therapy; substrate reduction therapy; gene therapy

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Introduction

Fabry disease (FD; OMIM 301500) is an X-linked (Xq22.1) lysosomal storage disorder taking origin in enzyme deficiency of the α-galactosidase A (enzyme commission no. 3.2.1.22) (1). This results into accumulation of globotriaosylceramides (Gb3) and the derivative globotriaosylsphingosine (lyso-Gb3) in all lysosome carrying tissue. Clinically, phenotype expression is prominently accompanied by cardiac, renal and neurological impairments including young-aged cryptogenic stroke, chronic kidney disease, and a variant of hypertrophic

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cardiomyopathy complicating with ventricular tachycardia and sudden cardiac death (1,2).

Until 2001, no specific therapy was available accounting for poor prognosis especially in classical disease variants with multisystem manifestations (3). The introduction of enzyme replacement therapy (ERT), first approved in 2001, led to a significant improvement of complication rates and early death. However, some patients deal with insufficient response to therapy or antibody-related adverse events. Unfortunately, all benefits of ERT might come along with degrading quality of life due to the need of intravenous application. Thus, the first oral Fabry-specific drug in form of the chaperone *Migalastat* (Galafold®, Amicus Therapeutics, USA) marked a further step to improved treatment options in FD. Dynamic drug development has ever since continued including substrate reduction and novel second-generation ERT agents waiting in line. Finally, gene therapy is moving forwards and first preliminary data has been presented. This review summarizes to date long-term results on first-generation ERT, the current state-of-the-art therapeutic options and gives a glimpse into the nearby future on Fabry-specific drugs. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/cdt-20-743).

Methods

We conducted a comprehensive systematic literature review considering literature in English and German language of articles on treatment of FD published up until April 2020 available on PubMed (https://pubmed.ncbi.nlm.nih.gov). Key words: Fabry disease; enzyme replacement therapy; chaperone therapy; substrate reduction therapy; gene therapy;

Current treatment options

In 2020 there are two different Fabry-specific therapy approaches with three drug agents available outside of ongoing clinical trials. Long-term data on efficiency and complications of ERT are broadly available, whereas real-world data on the relatively new oral chaperone still remain restricted to relatively short time frames.

Long-term results on first-generation ERT

Available since 2001, ERT has been the first commercially available Fabry-specific drug therapy. Almost 20 years after its first approval in Europe, several studies reporting long-term data on clinical outcome of first generation ERT have been published aiming to provide clinical guidance on the optimal time of initiation and dosage (4).

Currently, two recombinant ERT agents are approved and aim to supplement the either insufficiently available or defectively produced physiologic human α-galactosidase A. While *agalsidase alfa* (Replagal®, Takeda Pharmaceutical, Tokio, Japan) is produced using human fibroblast lineages and administered in a dose of 0.2 mg/kg bodyweight, *agalsidase beta* (Fabrazyme®, Sanofi Genzyme, Cambridge, MA, USA) is usually administered in a dosage of 1.0 mg/kg and is produced using Chinese hamster ovary cells. Both agents are advised to be given intravenously every other week and have been shown save in various randomized controlled trials (3,5-10).

Eng *et al*. reported that ERT leads to Gb3-deposition clearance in glomerular endothelial cells, which corroborated to clinical data indicating a significant reduction in occurrence of Fabry-associated events in patients undergoing ERT (11). Hughes and colleagues reported that initiation of agalsidase alfa led to a significant increase of the glomerular filtration rate indicating good therapeutic response of renal organ involvement (7). Other publications reported a slowed but progressive decline in glomerular filtration rate following ERT initiation (12-18). While the occurrence of albuminuria has effectively been prevented in patients negative for proteinuria at point of ERT-initiation, it was reported to persist in those with pre-existing albuminuria (19). Thus, therapeutic success seems to be patient- and case-depended varying from either improvement, stabilization, or further decline of kidney function. Similar results were reported for cardiac organ involvement with left-ventricular hypertrophy declining, stabilizing or proceeding on a case-dependent level (16,20). Several studies indicate that ERT shows its best therapeutic potential in preventing disease progression and development of clinically relevant end-stage complications if started at early stages of disease where no irreversible organ damage has yet been set, while late therapy initiation might result in a diminished therapy efficacy (21-24). In this regard, Germain *et al*. reported that patients with no evident chronic kidney disease benefited more from agalsidase alfa therapy than patients presenting manifest kidney injury at point of ERT initiation (21). Similar results were published for cardiac organ involvement, were therapeutic effect was lower in patients presenting myocardial fibrosis at point of initiation (24). Furthermore, a multi-center study

comparing lyso-Gb3 decrease after ERT initiation in men with classical FD who started ERT before *versus* after age 25 years, showed that early therapy initiation resulted into better biochemical response (23). As plasma lyso-Gb3 has been shown correlating with clinically feasible severity of FD, it seems to be a reliable biomarker besides of Gb3 deposition clearance on a histological level and thus presumably a valid indicator of therapy success, respectively failure (25,26). While a trend towards a reduction of plasma Gb3 and lyso-Gb3 levels has been reported for both currently available ERT agents (6,21,27-36), some data have indicated a higher potential on a significant reduction observed in patients treated with agalsidase beta compared to agalsidase alfa therapy (27,28,30). A potential positive impact of dose increase or regime change into weekly infusions was neglected by Schiffmann *et al*., who reported no significant impact on plasma Gb3 levels following intensification of therapy intervals to 0.2 mg/kg or even 0.4 mg/kg agalsidase alfa once per week (37,38).

Beginning in June 2009, viral contamination of agalsidase beta production facilities resulted into a worldwide drug shortage implying 'drug holiday', dose reduction, or product switch in most patients with FD who had previously received agalsidase beta therapy (39,40). Many of those patients who had previously received the regular dose of 1.0 mg/kg every other week now underwent dose reduction to 0.3–0.5 mg/kg agalsidase beta, or were switched to agalsidase alfa (40). Especially the latter was controversial, as clinical experience on ERT regime changing was very limited by then (17,41,42). While some studies indicate kidney function deterioration following therapy alterations in patients who had previously been stable on ERT (40,43,44), others discuss a neutral or clinically non-relevant impact of dose change, respectively therapy switch in patients with FD. Even though short-term observation by Smid *et al*. did not reveal an increase in adverse events after dose reduction to 0.5 mg/kg, an increase of lyso-Gb3 levels still indicated a rising disease activity (17). However, the latter has not been confirmed by other studies (29,45,46). In 2017, Pisani *et al*. performed a meta-analysis on seven studies focusing on the effects of therapy switch and in fact did not observe any significant differences in renal function during follow-up (47). In part contradictory results were observed in regard of cardiac organ manifestations and function deterioration, which however overall also remained stable with no clinically relevant disease progression being triggered by therapy alterations (45-47).

In conclusion, individual response, therapy success and disease-progression might significantly vary on a case-to-case basis with personal risk factors, such as genotype, age and gender, time of ERT-initiation, the patients' personal disease activity, and phenotype expression potentially serving as disease-modifying factors indirectly influencing therapeutic success (3,22). Finally, positive effects of first-generation ERT come along with the burden of biweekly infusions and potentially severe directly infusion-related side effects (48). Anaphylactic or anti-drug antibody mediated reactions may indeed result into clinical complications in rare cases (3,49-54).

Chaperone therapy

Limitations of ERT, such as its inability to cross the blood-brain-barrier, and the burden of intravenous application has emphasized the need of new, preferably orally available Fabry-specific drugs. This demand was pleased in 2016 with the introduction of the first-in-class chaperone agent *Migalastat* (Galafold®, Amicus Therapeutics, USA). Chaperones are small molecules binding and stabilizing the modified alpha-galactosidase A in amenable mutational variants of FD. Hereby, it facilitates lysosomal trafficking and increases lysosomal enzyme activity subsequently enhancing enzymatic degradation of Gb3 into excretable form of Gb2 (55,56). In order to evaluate whether a pathogenic mutation is amenable to chaperone therapy, a Migalastat-specific assay measuring Migalastat-induced changes in human embryonic kidney (HEK) cells are transfected with DNA plasmids containing pathogenic *GLA* variants (56). The criteria for amenability were defined as an increase of enzyme activity by at least 1.2-fold above the baseline value, with an absolute increase of at least 3% compared to wild type enzyme activity (56). After a *GLA* variant has been tested once, all results are available in a public database (www.galafoldamenabilitytable.com), allowing physicians a simple and efficient planning of therapy.

In the phase III licensing trial, Germain *et al*. reported that among the randomly assigned patients with amenable mutations, left ventricular hypertrophy decreased significantly within the interventional arm. Furthermore, unspecific but Fabry-associated symptoms such as diarrhea, reflux, and indigestion decreased. The slight decrease in glomerular filtration rate can be argued to be within physiological ranges, however, indicating no strong benefit regarding renal organ involvement of respective patients under observation (57).

Hughes *et al*. compared ERT with chaperone therapy in the phase III ATTRACT study. 57 Fabry patients (44% male) on stable ERT were randomized to switch to Migalastat for 18 months or stay on ERT. A significant decrease of left ventricular mass index (measured via echocardiography) was reported for the Migalastat group (n=34). Migalastat and ERT had identical effects on renal function and lyso-Gb3 levels (58).

In the extension of the phase III FACETS trial, Germain *et al*. reported clinical benefit of Migalastat especially for male Fabry patients with classic phenotype. After 24 months, activity of alpha-galactosidase A increased, renal function was stabilized and left ventricular mass index was reduced in a subgroup of the FACETS trial (59). However, the examined group of patients was small (n=14) and included only male patients with classic phenotype compared with a subgroup of nearly exclusively female patients (n=36). Therefore, results should be interpreted carefully.

Even though the data published within the described randomized trials indicated a strong benefit especially regarding cardiac organ involvement, many aspects of the heterogeneous disorder FD remain unaddressed. Real world data from patients treated with the commercially available drug have shown that there might be specific positive effects in the myocardium exceeding positive ERT effects, such as reverse remodeling with a decrease in myocardial late enhancement in cardiac magnetic resonance imaging after initiation of treatment (60). However, the question which patients might benefit most from chaperone—specifically in direct comparison to ERT—is still mostly unanswered. Importantly, it has been shown that also among the amenable patients there can be vast differences in biochemical response to therapy, ranging from normalization of enzyme activity to only marginal changes *in vivo* (60,61). In a monocenter real world collective, median enzyme activity increased rapidly from 29% to 44% of the normal wild-type activity (P=0.01). Plasma lyso-Gb3 levels at one year were stable with a tendency for reduction in both females (P=0.35) and males (P=0.20), while a reduction of GFR over the first year of treatment was seen [creatinine: 0.94 (IQR 0.81–1.09) *vs*. 1.0 (IQR 0.77–1.18); P=0.021] (61). Interestingly, at one year, enzyme increase in patients correlated with myocardial mass reduction (r=–0.546; P=0.044), but not with renal function (r=–0.086; P=0.770) (61,62).

To better evaluate the safety along with cardiovascular, renal and patients-reported outcomes and disease biomarkers under real world conditions, a prospective multicenter observational study was initiated as early as 2017 (63). The results from 59 (28 females) patients with amenable mutations following twelve months of chaperone therapy strengthen the preliminary results from clinical trials and single center experience regarding therapeutic effectiveness, especially in regard of cardiac organ involvement. Oral Migalastat therapy was generally safe with no severe adverse events occurring within the 12-month observational period. In detail, female as well as male patients both showed a significant reduction of left ventricular mass index, which had been predefined as primary endpoint (63). The glomerular filtration rate slightly decreased over the first year of therapy in concordance to the licensing trial (57).

Of note, the irregular intake every other day leads to different days of therapy every week. Therefore, an estimation of adherence control in patients with Migalastat is required implicitly. The ongoing MALTA study (NCT03683966) investigates therapy adherence of Fabry patients receiving chaperone therapy. Further long term data are to be obtained in order to finally evaluate the definitive value, benefits, and potentially also risks of Migalastat therapy as compared to ERT, the therapeutic approach with longest experience so far.

Adjunct therapy

Besides the disease-specific therapeutics listed above, a broad spectrum of non-specific adjunct therapies are applied regularly in patients with FD (*Table 1*). These not only include non-FD-specific drugs, but also non-pharmacological therapeutic interventions such as renal replacement or cardiac device therapy.

Due to their reno- and vasculoprotective effects, many FD patients require angiotensin converting enzyme inhibitors (ACEi), respectively angiotensin receptor II blockage (ARBs) in case of hypertension or proteinuria and still compensated kidney function (64). Warnock and colleagues showed that the additional application of ACEi/ARBs resulted into a significant antiproteinuric effect in patients with severe Fabry nephropathy who were undergoing enzyme replacement therapy (65). However, as these agents do not address the underlying pathophysiologic mechanisms including Gb3 accumulation in podocytes, the long-term positive effect of ACEi/ARBs remains speculative and most likely largely dependent on the success of the Fabry-specific therapy (66). In end-stage Fabry nephropathy, renal replacement therapy including

Table 1 Excerpt and overview on basic treatment of Fabry disease

Type	Agent/method	Dose	Administration	Interval	Class	Comment
Non-specific treatment of organ complications						
Cardio-vascular						
Heart failure medication	ACEi/ARBs; aldosterone antagonists (diuretics, betablockers, sacubitril/valsartan)	diverse	Per os	Daily	I A	Heart failure medication according to current guideline recommendations. As most patients demonstrate heart failure with preserved ejection fraction, therapy should be orientated on respective recommendations. ACEi/ARBs are the most common non-specific medication in Fabry disease and are often initiated at early stage due to their additional renoprotective effect; experience with sacubitril/valsartan still scarce in Fabry disease
Cardiac device therapy	Loop recorder, pacemaker, implantable cardioverter defibrillator	NA	Operative	Once	I C	For detection/therapy of atrial/ventricular arrhythmia and prevention of sudden cardiac death; Case-to-case decision depending on patient-specific factors such as underlying genotype, phenotype expression, History of prior arrhythmia events, family history for sudden cardiac death, extend and course of cardiomyopathy; expert opinion; no guideline recommendations available
End-stage heart failure therapy	Cardiac assist devices (e.g., LVAD); heart transplantation	NA	Operative	Once	I C	In end-stage heart failure; treatment according to current guideline recommendations; no explicit guideline recommendation available for Fabry disease
Secondary prevention of stroke	Acetyl silicic acid/ anticoagulation therapy; consider further therapeutic options if indicated e.g., PFO closure	NA	Diverse	Diverse	I C	Even though the exact pathomechanism of stroke remains unknown, patients should be treated to well-established guideline recommendations of stroke. Consider further diagnostics and interventions (e.g., PFO-closure), where indicated
Renal						
Treatment of proteinuria	Low protein diet	NA			I A	According to guideline recommendations
	ACEi/ARBs	diverse	Per os	Daily	I A	Preventive in patients with renal organ involvement/proteinuria and compensated glomerular filtration rate
Renal replacement therapy	Dialysis		Intravenous	3 times per week	I A	In end-stage Fabry nephropathy; bridging to kidney transplantation; according to guideline recommendations for kidney failure; no Fabry-specific guideline recommendations available
	Kidney transplantation		Operative	Once	I C	Unfortunately the strive for kidney transplantation cannot always be fulfilled due to waiting lists and/or relevant comorbidities/other severe organ involvement

Table 1 (*continued*)

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Type	Agent/method	Dose	Administration	Interval	Class	Comment
Pain						
Intensified pain therapy	e.g., neuropathic pain medication	diverse	Per os	Daily	I C	According to expert opinion; Due to clinical and therapeutic complexity, patients should be treated by neurologist with experience in the field of Fabry-associated and neuropathic pain
Currently available disease-specific therapeutics						
Enzyme replacement therapy	Agalsidase alfa (Replagal®)	0.2 mg/kg	Intravenous	14 days	I A	Should be initiated and re-evaluated on an annually or every other year basis by specialized centers
	Agalsidase beta (Fabrazyme®)	1.0 mg/kg	Intravenous	14 days	I A	Should be initiated and re-evaluated on an annually or every other year basis by specialized centers
Chaperone therapy	Migalastat (Galafold®)	123 mg	Per os	Every other day	I A	Should be initiated and re-evaluated on an annually or every other year basis by specialized centers. Instead of enzyme replacement therapy; only available for patients with amendable mutations (www.galafoldamenabilitytable.com). No long-term data available, since only available since 2016
Emerging disease-specific therapeutics (not yet approved)						
Pegylated enzyme replacement therapy	Pegunigalsidase alfa®	NA	Intravenous	Once per month (aimed)	NA	Aiming higher therapeutic effect and thereby extend of therapy intervals compared to first generation enzyme replacement therapy. Ongoing clinical trials
	moss-aGal®	NA	Intravenous	NA	NA	Aiming higher therapeutic effect and thereby extend of therapy intervals compared to first generation enzyme replacement therapy. Ongoing early clinical trials
Substrate reduction therapy	Lucerastat®; Venglustat®	NA	Per os	Daily	NA	Ongoing clinical trials
Gene therapy	Various in development (none approved)		Intravenous	Once	NA	Experimental; pre-clinical and clinical trials are currently performed; Potentially interesting for patients with severe disease progression despite Fabry-specific therapeutics

hemodialysis and kidney transplantation are well-established treatment options with results comparable to those in other diseases (1,67,68).

Cardiac organ involvement and its clinical complications remain the main cause of premature death in FD, highlighting importance of cardiac interventions. Fabry cardiomyopathy is a common cause of heart failure typically starting in the 3rd or 4th decade in life. Systolic function is usually preserved until late stages where left ventricular ejection fraction drops due to progressive scaring. The whole spectrum of heart failure medication might be applied taking into account clinical stage (69). Of note, betablockers are often not well tolerated by the patients, probably due to neurohumoral dysregulation. While aldosterone antagonists are well established, experience and long-term effects of novel therapeutics such as sacubitril/valsartan are still limited in FD. Rhythm disorders are common, often resulting in the indication for pacemaker implantation. Despite the positive effects of Fabry-specific therapeutics, patients with advanced Fabry cardiomyopathy also still face a relevant burden of malign ventricular arrhythmia and sudden cardiac death. With only few published articles available, beneficial effects of implantable cardioverter defibrillator therapy remains inconclusive with no guidelines been established to date (70-73). This is of special relevance in those patients demonstrating with the "cardiac variants" where organ manifestations are almost completely limited to the heart. These patients often face a significant delay in identifying FD as underlying pathology, which can even worsen the risk of cardiac complications due to inadequate treatment (74). Clinical experience indicates that irreparable damage is often set at the point of FD diagnosis. Thus, the decision towards a recommendation of implantable cardioverter defibrillator therapy should be evaluated and discussed as a case-to-case decision especially in patients demonstrating with high-risk profile such as advanced Fabry cardiomyopathy with extensive replacement fibrosis, end-stage wall-thinning and/or prior ventricular tachycardia.

Clinical studies have also shown that FD is a relevant differential diagnosis in young-aged patients with cryptogenic stroke (75). In case of cerebrovascular events, diagnostic and therapeutic decisions should be performed according to current guideline recommendations for stroke (76). As treatment of Fabry-associated pain is complex, these patients should be referred to specialized neurologists for adequate pain therapy (77).

New drug developments

Second-generation ERT

While both first-generation lysosomal enzyme replacement agents are produced using mammalian cell lines, new "second-generation" ERT agents aim to overcome disadvantages of mammalian cell line production, including higher production costs and the risk of contamination by mammalian pathogens, and to extend therapeutic effects (78). As tissue uptake of intravenously applied enzyme replacement agents is usually performed though either the mannose or the mannose 6-phosphate receptor, it is assumed that these receptors might play a key role responsible for therapeutic efficiency of ERT in lysosomal storage disorders (78). Recent approaches aiming to establish lysosomal enzyme production in plant-derived cell lines have been reported before (79-81). For FD, two plant-derived ERT agents (*Pegunigalsidase alfa*®, Protalix Biotherapeutics, Israel; and *moss-aGal*®, Greenovation biopharmaceuticals, Germany) are currently tested in clinical trials.

Pegunigalsidase alfa intends to not only increase plasma half-life of infused recombinant enzyme, but also to further improve long-term therapeutic tolerance by reducing the formation of anti-drug immunogenicity through pegylation of the enzyme (82). Murine models underlined the aimed therapeutic effect by prevention of Gb3 accumulation in both cardiac and renal tissues (83). Furthermore, clinical phase I/II trials also reported a reduction of Gb3 accumulation in human glomerular biopsy tissue acquired by kidney biopsies (82). First preliminary data of the phase III BRIDGE trial (NCT03018730) report that therapy switch from agalsidase alfa to Pegunigalsidase alfa was save, well-tolerated and resulted into stabilization, or at least slower progression of kidney failure (eGFR slope improvement from –5.1 to 0.23 mL/min/1.73 m^2/year in both male and female) (84). Further results of currently ongoing clinical trials (NCT02795676; NCT03018730, NCT03180840) evaluating Pegunigalsidase alfa treatment are expected to be published soon.

Different to the currently available mammalian cell based ERT agents, moss-aGal does not rely on mannose-6-phosphate receptor mediated endocytosis but targets the mannose receptor for tissue uptake (85). Shen *et al*. evaluated the effectiveness of a non-phosphorylated α-galactosidase A produced from moss (thus referred as "moss-aGal") in an in-vitro and in-vivo mouse model of FD (78). Their key findings were that (I) endocytosis of moss-aGal

was mannose receptor-mediated and dependent, (II) moss-aGal was more preferentially targeted to renal cells than agalsidase alfa, (III) a single injection of moss-aGal resulted into a comparable substrate clearance in both cardiac and renal tissue as perceived in agalsidase alfa (78). Hennermann *et al*. conducted a phase I clinical trial evaluating moss-aGal therapy in six patients receiving a single dose of 0.2 mg/kg moss-aGal (86). In all patients, single dose moss-aGal application was well tolerated and showed a reduction of both plasma lyso-Gb3 levels (–3.8%) and urinary Gb3 levels (up to –60%) after 28 days (86). Currently phase II/III trials further investigating this promising novel ERT-agent are in preparation.

Substrate reduction therapy

In contrast to currently available medication, substrate reduction therapy (SRT) neither aims to replace the insufficiently available or dysfunctional enzyme, nor to improve its activity by refolding. Instead, it blocks the emergence of Gb3 overload as well as its accumulation at an earlier step, namely at its point of production. Importantly, its therapeutic effects might also result into adverse events, as too intense abrogation of enzymatic reactions might result into homeostatic imbalance as discussed before (87). However, from the current point of view the unique selling point could become the ability of passing the blood-brain barrier, subsequently preventing cerebrovascular events, which to date remains an unmatched goal in Fabry-specific treatment (88). Two different SRT molecules (*Venglustat*®, Sanofi Genzyme, Massachusetts, USA; and *Lucerastat*®, Idorsia Pharmaceuticals, Switzerland) have been developed for disease-specific treatment of FD and are currently evaluated in both pre-clinical and clinical trials (89-91). While Venglustat is still at an early stage of approval and only few data has been published so far. Preliminary data suggest a slow but gradual clearance of Gb3 from superficial skin capillary endothelium and a gradual decrease of plasma lyso-Gb3 in most therapy-naive patients (92). Lucerastat is currently undergoing clinical evaluation in the randomized multi-center double-blind clinical phase III MODIFY-trial (NCT03425539) (93). Promising initial results from phase I/II clinical trials show that therapy with lucerastat has been save with no clinically relevant safety abnormalities observed over a 12-week long oral application (93). Furthermore, a significant decreased of plasma glycosphingolipids, glucosylceramide, lactosylceramide, and globotriaosylceramide compared to baseline values were observed rising hope for future application (93).

Both novel SRT agents are promising potential oral therapeutics for the nearby future with no limitation regarding specific mutations as seen in chaperone therapy.

Gene therapy

The strive for a curative therapy of FD intensified the efforts of enabling gene therapy over the last years. Different viral vectors have been tested and first FD patients already treated within early clinical phase I/II trials (NCT02800070; NCT03454893) (94). Current approaches comprise re-administration of lentiviruses-transfected haematopoetic stem cells (NCT02800070; NCT03454893), adeno-associated viral gene therapy (*FLT190*®, Freeline therapeutics, UK; and *ST-920*®, Sangamo Therapeutics) and micro-RNA based therapy (Moderna Inc; Translate Bio) (95-100). The first reports available so far have shown that the concept in general is valid, leading to a prompt substantial rise of alpha-galactosidase A levels in the first patients after treatment. However, it currently remains largely unclear whether these initial effects will be long-lasting, or repetitive gene therapy will be needed. Future results of further clinical trials will further evaluate benefits but also risks, such as the development of neutralizing antibodies and immunologic reactions.

Summary

Treatment of FD in an exceptionally dynamic field with various new therapy approaches either already tested in clinical trials or arising in the near future. While ERT has proven its positive effects over many years, the availability of the first oral drug has led to a significant improvement at least of quality of life in many patients with FD already. However, due to amenability limitations, this approach is not an option for all patients with FD, currently leaving ERT essential as the only specific therapeutic option in most patients. Based on long-term experience and observational data from more than 20 years, early therapy initiation—before irreversible organ damage has occurred—is critically important, irrespective of the type of therapy chosen. Due to the rarity of FD, heterogeneity of the disease, and high therapy costs, therapeutic options should be thoroughly examined and re-evaluated annually thereafter in a specialized Fabry center, carefully taking the

various factors such as individual risk, efficacy of therapy, and quality of life into account. With novel therapy options such as oral drugs but also gene therapy just arriving, this aspect becomes even more relevant in the future.

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