Long Term Treatment with Enzyme Replacement Therapy in Patients with Fabry Disease

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Introduction

Anderson-Fabry disease (FD) is an X-linked lysosomal storage disorder based on private pathogenic mutations in the alpha-galactosidase A (α-GAL) encoding gene (GLA) [1]. In respective males with a classic mutation, a very low or completely missing α-GAL enzyme activity is apparent [1, 2]. As a result, progressive globo- triaosylceramides (Gb3) accumulation in lysosome-carrying tissues lead to irreversible and disease-specific tissue injury of the kidneys [3], heart [4] and equivalent alterations affecting the central and peripheral nervous system [5, 6] (fig. 1). Severity and prognosis vary individually due to gender, genotype and whether therapy is received or not [1, 7–11]. Without treatment, called natural history, a relatively poor prognosis is seen in male patients, usually leading to death in the fifth decade of life due to continuous disease progression [12]. Sudden cardiac death, end-stage kidney disease and strokes were...
Fig. 1. Representative illustrations of clinically relevant brain and heart organ involvement in patients with Fabry disease. Please note that ERT has limits in fully protecting patients from disease progression and harmful events, especially when started after a specific injury has already taken place. **a, b** Brain MRI scans reveal ischemic stroke in the region of the posterior cerebral artery of a 44 year old male Fabry patient who had received ERT for more than eleven years prior to the event. **c, d** Cardiac organ involvement in a 55 year old male patient who had been diagnosed with already advanced stage cardiomyopathy and later on died due to sudden cardiac death after receiving ERT for seven years. Two-dimensional echocardiography reveals typical cardiac hypertrophy (c) and speckle tracking analyses indirectly illustrate myocardial fibrosis visualized by bulls eye method (d).
among the most frequent causes of death during the natural history period before the year 2000.

With the advent of the first causal therapy in form of enzyme replacement therapy (ERT), legitimate hope was generated to overcome serious clinical complications and early death.

Fifteen years later, evidence emerges that the impact of ERT on life expectancy and quality of life is limited in many affected patients. In young patients ERT, if handled properly by multidisciplinary teams, still offers opportunities to control the many clinical pathologies. Noteworthy are the early detection and screening programs which also give rise to the assumption of higher incidences of the disease than previously assumed [13, 14]. However, as not all pathogenic classified genotypes result in clinically relevant organ injuries and associated symptoms, experts struggle with general and uniform treatment recommendations preferring personalized and patient-centered therapy concepts. With the upcoming availability of better tools for risk stratification and treatment option, individualized therapy of FD is anticipated as the new standard of care today.

Natural Evolution of FD

Despite the early description of the disease, there was no access to any Fabry-specific therapeutic option until the year 2001. In this pre-ERT era, especially hemizygous males were at high risk of developing chronic kidney disease (CKD) at a particularly young age. Branton et al. [15] presented data of 105 male subjects of whom 50% showed non-nephrotic range proteinuria and 20% had early-stage CKD (stage ≤3). At 50 years, a total of 27% reached end-stage kidney disease with the demand of renal replacement therapy. Only every second patient lived beyond the age of 55 years, and all had died before reaching the age of 60 years [15]. Facing these results, it is of no surprise that kidney organ injury has long been seen as the dominant burden leading to reduced life expectancy [15, 16]. Newer findings now suggest that cardiac complications are the leading cause of premature death today [12].

Long-Term Treatment Results of ERT

ERT was first introduced in the year 2001 and represents the current standard-of-care therapeutic option. Functionally, it aims to provide the pathologically missing or functionally impaired α-GAL by biweekly intravenous administration of recombinant human alpha (Replagal®, Shire) or beta (Fabrazyme®, Genzyme/Sanofi) galactosidase A. Clinical safety has been shown for either medication in various randomized controlled trials [17–22]. Yet potentially harmful anaphylactic and anti-agalsidase antibody-related reactions are also known [23–27] and continue to occur in daily clinical practice. Recently published studies prove the positive effects of ERT with yet most beneficial results being observed when ERT is started at young age, especially before irreversible organ injury may limit therapy outcome [28]. Fitting this, Germain et al. [28] reported that patients with no CKD benefited from Fabrazyme® treatment, whereas those who started ERT with apparent kidney injury proceeded as observed during natural course. Weidemann et al. [29] highlighted that patients achieved the best long-term improvement in myocardial morphology and function and exercise capacity when ERT was started before myocardial fibrosis was detectable by standard diagnostic procedures.

In 2009, an acute shortage of Fabrazyme® supply occurred due to viral contamination of the production facility, resulting in ‘drug holiday’, a dose reduction or product switch in most patients [30, 31]. Despite the fact that this situation meant substantial unpleasantness to many affected patients treated, it has provided a major gain of knowledge regarding the comparability of effectiveness and impact of dose reduction and switching between both available ERT products. Fortunately, Fabrazyme® dose reduction and switching to Replagal® is generally safe but both appear to come along with a burden of more advanced disease progression when compared to groups who continued with regular dose Fabrazyme® [31].

Limitations of Treatment through Antibody Development in ERT

In spite of benefits derived by both patient reports and randomized clinical trials, ERT is accompanied by anti-agalsidase antibody-mediated side effects and reactions [23–27]. As early as in 2004, Linthorst et al. [25] first investigated emergence and properties of antibody-mediated side effects. In a cohort of 18 patients who received ERT, 11 out of 16 men (69%) showed high titers of IgG antibodies cross-reacting with both recombinant enzymes in vitro whereas female subjects did not. Furthermore, the study findings suggested that anti-agalsidase A antibodies did neutralize the given recombinant ERT in...
vitro. Patients who had antibodies showed a significantly higher level of Gb3 in urinary samples than non-antibody patients, indicating a loss of ERT efficiency in patients displaying antibodies. Five years later, Bénichou et al. [23] published a retrospective analysis about the impact of IgG antibodies on therapeutic efficiency of agalsidase beta in FD. Contrary to the findings of Linthorst et al. [25], their study did not find a significant correlation between the occurrence of IgG antibodies and an abnormal elevation of urine Gb3 or the worsening of renal function. However, a higher amount of Gb3 deposition in dermal capillary endothelial cells was detected, which might indicate that IgG agalsidase A antibodies could take an impact on organ impairments at least in the long run [23].

With reference to antibody-mediated anaphylactic reactions, Tesmoingt et al. [27] reported about a male patient who did receive agalsidase alpha for more than 1 year before suffering from ERT infusion-related signs and symptoms leading to the need of systemic steroids and antihistaminic therapy intervention. Serum IgE antibodies testing and skin test reactivity to agalsidase beta were both described negative. After a therapeutic pause, a second therapy attempt now using agalsidase beta was performed, again leading to an anaphylactic shock. ERT was stopped and the respective patient only treated with symptomatic – yet not FD-specific – additive therapy. Negativity of immunological tests did not rule out the risk of repetitive anaphylactic shock following ERT [27]. Tanaka et al. [26] reported a similar case with more positive results in IgE testing, indicating that IgE antibodies against agalsidase beta can indeed be developed, with potential cross-activity to agalsidase alpha.

To date, the reliable detection and conclusive evaluation of a potential impact of IgE and IgG antibody-mediated reactions and reduced therapeutic effectiveness of ERT remains incompletely understood. More precise standardized testing procedures need to be established, which might highly influence how we treat FD in the near future. Furthermore, ERT has only limited benefit for prevention of cerebrovascular events [28, 32–34].

**Supportive Organ-Specific Aspects in Treatment of FD**

In general, there are no specific therapeutic limitations regarding patients with FD. As baseline therapy, respective patients should be treated similar to patients with cardiomyopathies, CKD or stroke of other origin.

**Chronic Kidney Disease**

Many patients who approach specialized centers today have been originally identified throughout family screening with no pathologic proteinuria present. By progression of Gb3 accumulation in renal tissue, mild proteinuria might be detectable leading to recommendation of renoprotective medication as used in the vast majority of kidney diseases. Patients presenting an early stage of Fabry nephropathy might benefit from angiotensin receptor or angiotensin-converting enzyme blockage, which should be generally considered in all affected patients [35].

**Cardiomyopathy**

Patients with advanced stages of cardiac involvement show characteristics of heart failure with preserved ejection fraction, with the potential to progress toward a reduction of cardiac function [36]. This proposed end-stage complication is actually only rarely seen in clinical practice as affected patients are more likely to suffer from malignant (tachy-)arrhythmia events prior that resemble the leading cause of reduced life expectancy today. Thus both, anti-arrhythmic/frequency controlling and congestive heart failure medications are cornerstones of adjunc- tive treatments. As we have recently shown, patients might benefit from early cardiac device therapy including loop recorders for detection of arrhythmia and prophylactic implantable cardioverter defibrillator implantations for prevention of life threatening ventricular tachycardia [37–39].

**Fabry-Associated Pain**

Fabry-associated pain is often very complex and difficult to cope, requiring extensive assessment by specialized neurologists [6, 8]. Neuropathic origin is regularly hypothesized [40] potentially explaining why patients might not respond to therapy with non-steroidal anti-rheumatic and/or non-opioid analgetic drugs, but from medications as pregabalin, carbamazepines or tricyclic antidepressants [41]. The results of placebo-controlled trials suggest that ERT significantly improves Fabry-associated pain, but were somehow inconclusive regarding the question of the underlying mechanism, as not only patients in the intervention but also some in placebo groups reported less pain indicating an unspcific, maybe even psychologically influenced benefit when being under closer observation [21, 42].
Further Impairments and Accompanying Comorbidities

Many patients attract attention during their school years with low performances, fatigue and school attendances, potentially improved by ERT [22, 43, 44]. Non-specific gastrointestinal impairments such as frequent diarrhea, abdominal cramping and pain are frequently reported by many patients with only little knowledge on ERT effects available [45, 46]. Interestingly, lactose intolerance seems to be frequent in Fabry disease with respective patients benefiting from adaption of food consumption [8]. Vitamin D deficiency is also known to show high prevalence and was strongly associated with the stage of Fabry cardiomyopathy and occurrence of adverse clinical symptoms [47]. Whether vitamin D supplementation may improve complications would require a randomized controlled trial.

Emerging Therapeutic Concepts

Various new medications arise on the therapeutic horizon, which may lead to further improvements of symptoms and outcomes. The pharmacological chaperone Migalastat HCl (Galafold®, Amicus) is a newly approved oral treatment leading to enhanced plasma levels of agalsidase in disease-relevant tissues [48–50]. It is also expected to be beneficial in combination with classical ERT, assuring its future eligibility [48–50]. One limitation of chaperone therapy is the applicability to FD patients with specific GLA mutational variants, for example, N215S, P205T or R301Q [50, 51]. Due to its novelty, there are no long-term data available yet. Further promising interventions may be modified, pegylated, enzyme preparations or oral substrate reduction therapies in the future (fig. 2).

Summary

Today, ERT is the standard therapy and specific for FD with 15 years of clinical experience. It has variable effects on disease progression potentially protecting from end-stage irreversible organ injuries. The few randomized controlled trials with short-term follow-up during ERT or placebo treatment followed by a long-term open-label observational period report beneficial outcomes in younger patients as compared to older ones. When administered during early disease stages without organ morphologic equivalent, short-term observations lend to optimism of controlling the disease at the most appropriate point in time. The further ERT application is postponed, the less efficiently it appears to obtain an optimal treatment effect in respect to long-term survival. However, as biweekly ERT resembles a substantial cut in patients' individual quality of life, therapy induction should remain an individual decision well balancing the benefits and risk. As major limitation, ERT does not manage to completely protect from irreversible organ injury but is more likely to slow down progression.

Fig. 2. Overview on milestones and perspectives of Fabry-specific therapy concepts. Before the year of 2001, no Fabry-specific medication was available, leading to rapid disease progression as described for natural history period. Nowadays, scientific focus has been set on developing new therapeutic concepts e.g. orally available chaperone medication aiming to overcome current therapeutic limits.
Disclosure Statement

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Compliance with Ethics Guidelines

Studies were performed in accordance with the declaration of Helsinki and approved by the local Ethics Committee of the University Hospital Würzburg, Germany. All study patients gave written informed consent for scientific analysis and publication.

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