

Expert Opinion

1. Introduction
2. Review of agalsidase alfa
3. Expert opinion

Agalsidase alfa – a preparation for enzyme replacement therapy in Anderson–Fabry disease

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Anderson–Fabry disease is an X-linked multisystemic disorder caused by a genetic deficiency of the lysosomal enzyme α -galactosidase A. The enzyme is responsible for degradation of glycolipids inside the lysosomes. Lack of catalytic activity leads to progressive depositions of undegraded glycolipids in a large number of organs. Crises of severe pain in the extremities (acroparesthesias), hypohidrosis, corneal opacities and dysfunction of several organs (kidney, brain, heart) are the leading symptoms in patients with Anderson–Fabry disease. Females may have the same symptoms as males but to a more variable degree. The variable manifestations seen in heterozygotes can be explained by the Lyon hypothesis. This hypothesis predicts that in X-linked diseases, the carriers are a mosaic of normal and mutant cells in varying proportions and hence have variable expression. As in Gaucher's disease, enzyme replacement therapy recently became available for Anderson–Fabry disease. Two drugs have gained approval in the EU by the European Agency for the Evaluation of Medicinal Products. These are agalsidase beta (Fabrazyme®, Genzyme Corporation) and agalsidase alfa (Replagal®, Transkaryotic Therapies, Inc.). This review will describe clinical efficacy, safety and tolerability of agalsidase alfa.

Keywords: agalsidase alfa, Anderson–Fabry disease, enzyme replacement therapy, α -galactosidase A, lysosomal storage disorder

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1. Introduction

Glycosphingolipids are essential constituents of cell membranes and are widely distributed in human tissues. They consist of a hydrophilic complex carbohydrate chain and a hydrophobic ceramide. In ceramide, an amino alcohol (sphingosine) is acylated with a long chain fatty acid through an amide linkage (Figure 1). Many lysosomal enzymes are involved in the stepwise degradation of these sphingolipids. A genetic defect of one of these enzymes leads to disorders that are characterised by progressive storage in affected organs and functional impairment. For example, in Gaucher's disease, glucocerebrosidase is deficient leading to accumulation of glucosylceramide in different organs, predominantly in the spleen and bone marrow. Niemann–Pick disease is caused by the lack of activity of sphingomyelinase and is characterised by hepatosplenomegaly and, in most cases, also by neurodegeneration.

In Anderson–Fabry disease, glycosphingolipids with terminal α -galactosyl moieties, predominantly globotriaosylceramide (Gb₃) and to a lesser extent, galabiosylceramide and blood group substances, are accumulated in a variety of cell types due to the genetic defect of the lysosomal enzyme α -galactosidase A [1]. The progressive deposition of storage material in endothelial cells, smooth muscle cells of blood vessels, ganglion cells and many cell types of the kidneys, heart and eyes leads to a multisystemic disorder characterised by acroparesthesias, skin and eye abnormali-



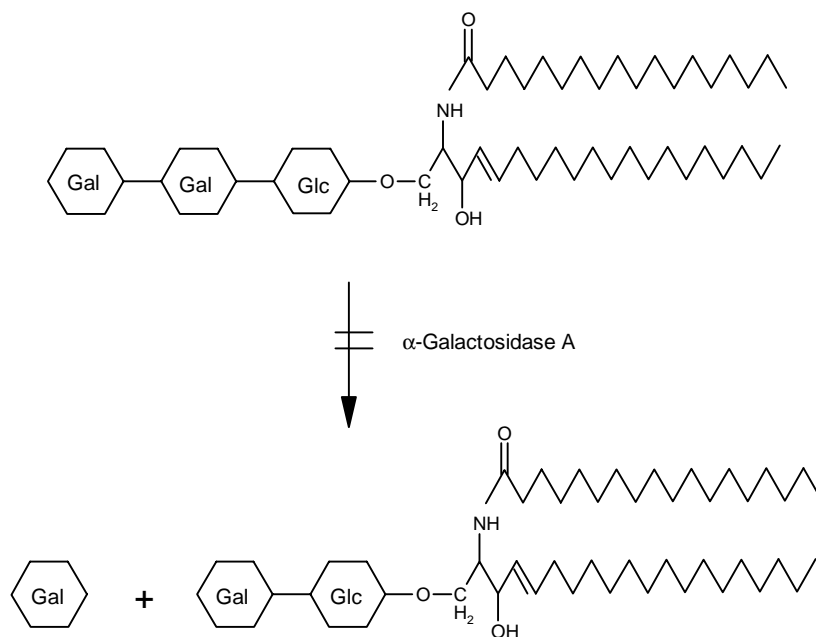


Figure 1. Degradation of globotriaosylceramide by the lysosomal enzyme α -galactosidase A. In Anderson–Fabry disease, this enzyme is deficient.

Gal: Galactose; Glc: Glucose.

ties, cardiomyopathy, kidney dysfunction and cerebrovascular complications.

The enzyme α -galactosidase A (α -D-galactoside galactohydrolase, E.C. 3.2.1.22) is a glycoprotein of ~ 101 kDa and has a homodimeric structure. It contains a 5 – 15% asparagine-linked complex and high-mannose oligosaccharide chains. The gene encoding α -galactosidase A maps to Xq22.11 and has a size of 12 kb. It contains seven exons varying in length of 92 – 291 bp. To date, > 200 mutations have been detected occurring randomly throughout the gene. Mutations that have been observed in affected families include large rearrangements, insertions, deletions and point mutations [2]. Total gene deletions have not been identified.

The enzyme α -galactosidase A must be discriminated from the enzyme α -galactosidase B (α -N-acetylgalactosaminidase, EC 3.2.1.49), which is genetically distinct and has different catalytic properties. Whereas α -galactosidase A splits galactose from substrates containing terminal α -galactosidic residues, α -galactosidase B is responsible for the degradation of substrates with α -acetylgalactosaminyl moieties. The deficiency of α -galactosidase B leads to the lysosomal storage disorder known as Schindler disease.

In males and females affected by Anderson–Fabry disease, first symptoms arise during childhood. Boys and girls complain of episodic crises of burning pain in hands and feet, that are often triggered by fever, exercise or emotional stress. Also abdominal pain may be reported that may mimic appendicitis or renal colics. At the same time, in the skin punctate dark red

to blue-black angiectases (angiokeratomas) develop. These angiokeratomas are most commonly seen at the hips, back, thighs, buttocks, penis and scrotum. The oral mucosa and conjunctiva may also be involved. A very common symptom in affected males and females is hypohidrosis (reduced sweating) or even anhidrosis (inability to sweat) that can be explained by the accumulation of globotriaosylceramide in the dorsal root ganglia.

In the eyes, corneal opacities are seen by slit-lamp examination that appear as whorled streaks extending from a central vortex to the periphery of the cornea. These ocular changes do not impair vision.

After the age of 30 years, the major morbid symptoms of the disease result from the progressive glycosphingolipid deposition in the cardiovascular and renal system. Heart manifestation includes left ventricular enlargement, valvular abnormalities and arrhythmias. Cardiomyopathy and myocardial infarctions may lead to early death. Proteinuria represent the first sign of kidney involvement. In middle age, gradual deterioration of renal function leading to end stage renal failure takes place.

Cerebrovascular complications, such as transient ischaemic attacks, seizures, hemiplegia and labyrinthine dysfunction, are the consequence of multifocal small vessel occlusive disease. An extensive review of the symptomatology of Anderson–Fabry disease is given by Desnick *et al.* [3].

From recent clinical studies it has become clear that females are affected by Anderson–Fabry disease in the same

manner as hemizygotes, although to a more variable degree [4]. MacDermot and co-workers have found that the median cumulative survival in males with Anderson–Fabry disease was 50 years, which represents an ~ 20-year reduction of lifespan [5]. In affected females, lifespan was reduced to 70 years, which means a reduction of ~ 15 years in comparison with the general population.

The variable manifestation seen in heterozygotes can be explained by the Lyon hypothesis, which predicts that in X-linked diseases carriers are mosaics of normal and mutant cells in varying proportions. This assumption has been substantiated by the observation of female monozygotic twins who showed different phenotypic expression due to uneven X-inactivation [6].

The incidence of Anderson–Fabry disease has been calculated to be 0.21 cases per 100,000 live births (0.42 per 100,000 male live births) in the Netherlands [7] and to be 0.85 cases per 100,000 live births in Australia [8].

Until recently, only supportive therapy was available for individuals affected by Anderson–Fabry disease. Pain management has been shown to be very difficult and there is little relief for many patients, even those using a great number of analgesics. Sodium-blocking agents, such as carbamazepine and/or phenytoin, are commonly used. However, these drugs have been shown to be of poor therapeutic value in Anderson–Fabry disease and to treat pain effectively, often therapeutic levels above that generally used for treatment of epilepsy are required [9]. The episodes of pain may be treated by centrally acting narcotic analgesics such as morphine. Gabapentin, a recently introduced anti-epileptic drug used as an adjuvant in partial and secondarily generalised tonic-clonic seizures, has proven effective in neuropathic pain, such as diabetic neuropathy and post-therapeutic neuralgia [10].

The hypohidrosis (anhidrosis) can be managed by minimising intense physical exertion and having the patient work in a cool environment. Angiokeratomas can be removed by argon laser therapy, if desired for cosmetic reasons.

In patients with Anderson–Fabry disease renal insufficiency is the most frequent late complication. From a report given by Thadani and co-workers [11], the mean age of Anderson–Fabry patients that initiated dialysis was 42 years, 12% of these were female. In the Anderson–Fabry group, the 3-year survival was significantly lower than in non-diabetic controls. Given the poor survival on dialysis, alternative strategies must be considered to manage renal dysfunction. Kidney transplantation has been performed in a great number of patients and it could be shown that this procedure leads to correction of renal function, the engrafted kidney remaining free of glycolipid deposition for many years [12]. A kidney from a Anderson–Fabry heterozygote should not be transplanted as it may contain significant storage material resulting in renal dysfunction within a few years [13].

As soon as renal impairment develops, antihypertensive therapy must be initiated. This may also be necessary to treat cardiovascular complications. Prophylactic oral anticoagulants

are recommended for stroke-prone patients. At an early stage of disease the use of antiplatelet agents, such as aspirin, has been suggested as the glycosphingolipid accumulation in vascular endothelium activates platelets and increases angiogenesis. Coronary bypass procedures have been carried in Anderson–Fabry patients to treat severe coronary disease. In a 53-year-old female with end stage cardiomyopathy a heart transplantation was performed, 1 year after the grafting there were no clinical or histological signs of heart involvement [14].

As mentioned above, the storage process in the heart may also affect the conduction system leading to arrhythmias or complete atrioventricular block and/or sinus node dysfunction. If these complications arise, the insertion of a pacemaker may become necessary.

In summary, Anderson–Fabry disease is a multi-systemic disorder with involvement of several organs, including the kidney, heart and cerebrovascular system. Appropriate treatment can be carried out only with close cooperation of several specialists, including a cardiologist, a nephrologist and a neurologist.

2. Review of agalsidase alfa

2.1 Overview

Until recently, no effective treatment able to stop or even reverse the disease process of Anderson–Fabry disease was available. Many attempts have been undertaken to replace the defective α -galactosidase activity with normal enzyme. Early studies have demonstrated that α -galactosidase A, purified from plants [15] or human placenta [16], was internalised by skin fibroblasts from Anderson–Fabry patients and was capable of catabolising the accumulated substrate. In a clinical trial, enzyme obtained from human placenta and injected into two Fabry patients was shown to be metabolically active [17]. In a study performed by Desnick *et al.* [18], purified splenic and plasma forms of α -galactosidase A were administered to the patients and it could be shown that both these forms differed in the clearance rates from the circulation and rate of substrate depletion. The splenic form, that contained only few sialic acid residues, was cleared from the circulation much faster ($t_{1/2}$ ~ 10 min.) than the plasma form ($t_{1/2}$ ~ 70 min.), that was enriched in sialic acid and phosphate residues. The isozymes also showed differences in the rate of substrate depletion. The administration of α -galactosidase A from human spleen resulted in a rapid decrease of plasma globotriaosylceramide, followed by a return to the preinfusion value within 2 – 3 h. The enzyme, gained from human plasma, led to a prolonged reduction of the circulating substrate and the substrate levels returned to preinfusion values only after 2 – 3 days. These results can be explained by the fact that desialylated glycoproteins are rapidly cleared from the circulation by hepatic uptake via specific receptors at the surface of the liver cells [19].

After these early clinical trials clearly demonstrated that multiple injections of α -galactosidase A led to a decrease of

plasma globotriaosylceramide, efforts were made to set up large-scale production of the enzyme using molecular genetic techniques. These endeavours ended in clinical studies that were performed by two different groups. In one double-blind, placebo-controlled study conducted by the Mount Sinai Study group [20], agalsidase beta was administered that was produced by Chinese hamster ovary (CHO) cells. This enzyme preparation has been demonstrated to be effective in clearing globotriaosylceramide from the vascular endothelium of the kidney after 20 weeks of treatment, as assessed by light microscopy. This clearance was achieved in 69% (20/29) of the treated patients but in none of the placebo patients ($p < 0.001$). This finding was further supported by a significant decrease in globotriaosylceramide inclusions in kidney, heart and skin. However, there were no statistically documented clinical benefits of agalsidase beta compared to placebo.

Schiffmann *et al.* [21] reported the results of a study that had been performed at the NIH. In this randomised trial, an enzyme preparation of human source (agalsidase alfa) was used. The primary end point (effect on neuropathic pain) was clearly attained, as the treated group showed a consistent and progressive decline in pain scores compared with placebo ($p = 0.02$). Furthermore, there were documented improvements in secondary end points, such as creatinine clearance, cardiac conduction and left ventricular mass. Based on the results of these clinical trials, both drugs gained approval in the EU in August 2001.

2.2 Agalsidase alfa

2.2.1 Chemistry

Agalsidase alfa is a human α -galactosidase A which is purified from the conditioned medium of a stably transfected human cell line. A series of five chromatography steps is used to purify the enzyme to homogeneity, followed by a viral filtration step. The mature enzyme was characterised by SDS/PAGE with silver stain, western blot analysis and N-terminal sequence analysis [22]. It has been demonstrated to be a glycoprotein consisting of a 100 kDa homodimer of two $\sim 50,000$ Da subunits. Post-translational modifications include the cleavage of a signal peptide sequence and the addition of three N-linked oligosaccharides. Using mass spectrometry, molecular masses of 46 – 55 kDa were found, indicating heterogeneous glycosylation. It was shown by a cell based internalisation assay, that appropriate post-translational modifications are present for internalisation and localisation to lysosomes.

The activity of α -galactosidase A is expressed in units, where one unit is defined as the amount of enzyme required to hydrolyse 1 nmol/h of 4-methylumbelliferyl- α -D-galactopyranoside substrate at 37° C.

As excipients, the finished product contains, besides the active enzyme, polysorbate-20, sodium chloride, sodium hydroxide, sodium phosphate monobasic (monohydrate) and water for injections.

2.2.2 Pharmacodynamics

The first clinical trial with highly purified human α -galactosidase A was performed by Schiffmann *et al.* [22]. Ten patients with Anderson–Fabry disease were treated with a single intravenous infusion of five escalating doses of the enzyme preparation. In this trial, it could be shown that α -galactosidase A was capable of reducing globotriaosylceramide levels in the liver and in shed renal tubular epithelial cells in the urine sediment. The average reduction in globotriaosylceramide was $\sim 30\%$ after a single enzyme dose. There was also a significant decrease in the excretion of urine sediment Gb₃ on day 28 after the α -galactosidase A infusion. This result is an indication of effective delivery of the enzyme to the renal tubular epithelial cells. Plasma Gb₃ was reduced at 7 days postinfusion but the change was not significant. The lack of significant reduction of Gb₃ in the blood may be explained by the rapid turnover of globotriaosylceramide in plasma. Furthermore, it should be noted that the enzyme is nearly inactive at plasma pH.

2.2.3 Pharmacokinetics and metabolism

In single-dose pharmacokinetic studies performed in animals, there was early distribution throughout the blood volume, followed by uptake into liver, spleen, lungs, heart, kidney and bone marrow within a few hours of injection.

Human pharmacokinetic data were obtained in a clinical study conducted by Schiffmann and co-workers [22]. Ten Anderson–Fabry patients received α -galactosidase A as an intravenous infusion of 20 min. The doses of α -galactosidase A were 0.3, 0.6, 1.2, 2.3 and 4.7 units/kg of body weight. Each enzyme dose level was administered to two patients. At about 22 min postinfusion a peak in plasma concentration (C_{\max}) was found, with a T_{\max} of 20 – 24 min. Near the end of the infusion period, plasma concentration declined in a biphasic manner. The observed C_{\max} and also AUC_{∞} (total area under the curve) increased proportionally with dose. The apparent volume distribution at steady-state (V_{ss}) was 7.3 – 14.6 l (8 – 24 % of body weight). Clearance of administered enzyme ranged 1.3 – 3.1 ml/min/kg body weight with an average of 2.2 ml/min/kg. The terminal half-life ($t_{1/2}$) ranged 42 – 117 min, the average being 83 min.

In the six of the patients who received the three highest doses (> 1 unit/kg body weight) pharmacokinetic data were analysed by using a three-compartment model. By application of this model a good correlation between predicted and measured values was found. Furthermore, the substantial pharmacokinetic parameters (AUC , V_{ss}) generated from this three-compartment model were similar to those estimated by the non-compartmental model.

In liver biopsies taken 44 h after the enzyme infusion, ~ 8 – 32% of the total administered α -galactosidase A dose was still present; the higher the dose, the lower the relative uptake in the liver. Under the assumption that 50% of the administered dose reaches the liver (as it has been found in animals), an hepatic $t_{1/2}$ of > 2 days can be estimated. From

these results, it can be delineated that α -galactosidase A has a significantly longer half-life in tissue than in plasma, as it is characteristic of lysosomal enzymes. The estimated hepatic uptake for the recommended therapeutic dose of agalsidase alfa is 10%. In addition to the uptake of the enzyme in hepatocytes, uptake was also noted in Kupfer cells and endothelial cells demonstrating the diversity of cell types reached by the infused agalsidase alfa.

2.2.4 Clinical efficacy

Clinical efficacy has been shown in several studies. A double-blind, placebo-controlled trial (TKT 003) was conducted at the NIH. Twenty-six hemizygous male Anderson–Fabry patients, aged ≥ 18 years, took part at this study. Twelve doses were given, 14 patients received agalsidase alfa and 12 males were administered placebo. The main outcome measurement was the effect of the enzyme on neuropathic pain determined by question 3 ('pain at its worst' item) of the Brief Pain Inventory (BPI) while without neuropathic pain medication. In the agalsidase alfa group, mean BPI neuropathic pain severity score declined from 6.2 (0.46) to 4.3 (0.73) but there was no significant change in the placebo-group ($p = 0.02$).

Glomerular filtration rate was measured at baseline and at week 24 using inulin and creatinine clearance. In the placebo group, a threefold greater decline of inulin clearance was observed than in the treated group ($p = 0.19$). Analysis of creatinine clearance showed an improvement in renal function in the agalsidase alfa group compared with the placebo group. This improvement was largely accounted for by a more rapid deterioration of kidney function in the latter group. However, during the following open-label phase (study TKT 006), the decline in renal function was subsequently reversed in those patients who had received placebo in the double-blind phase (TKT 003).

The effect on the heart was determined by electrocardiography. There was a significant decrease in QRS-complex duration in the treatment group in comparison with the placebo group, where an increase was observed.

In addition to measuring clinical parameters, biochemical and histological investigations were also performed in the clinical trial TKT 003. In the treated group, plasma Gb₃ decreased from 12.4 to 5.58 nmol/ml, whereas in the patients receiving placebo an insignificant decrease (from 0.96 to 10.19 nmol/ml) was found. There was also a statistically significant decrease of urine sediment Gb₃ in the agalsidase alfa recipients ($p = 0.05$).

To examine changes in kidney histology, renal biopsies were performed at baseline and at week 24. The biopsies were assessed by renal pathologists who developed two classification systems to evaluate both changes in the glomerular architecture and in the tubulo-interstitial pathology. After 6 months of treatment with agalsidase alfa a clear improvement in glomerular histology was observed. There was a 21% increase in the fraction of normal glomeruli, whereas in the

placebo group, a decrease of 27% was observed ($p = 0.01$). No significant change in total score for tubulo-interstitial pathology was seen in the 6-month trial.

In addition to the histological evaluation, levels of Gb₃ were determined in the renal biopsy tissue. The patients randomised to the enzyme had a 21% decrease from baseline in their kidney Gb₃ levels, while patients who had received placebo showed a 4% decrease ($p = 0.27$).

In the clinical trial published by Schiffmann *et al.* [21], no echocardiographic or MRT studies of the heart were performed. However, it could be shown that enzyme replacement led to significant decrease in QRS-complex duration (from 94.1 to 91.7 ms) versus an increase from 94 to 97.6 ms in the placebo group. Kampmann *et al.* reported a rapid decline of left ventricular mass in 11 female patients who were treated with the enzyme preparation for 24 weeks [23].

In Anderson–Fabry disease, deposition of the storage material not only occurs in the skin, kidney and heart but also in the cerebral vasculature, with more localised involvement of central neurons together with dorsal root and autonomic ganglia in the peripheral nervous system. The extent of the cerebrovascular manifestation, best observed in T2-weighted MR sequences, increases with age [24]. By using different methods (PET with [¹⁵O]H₂O or transcranial Doppler) it has been demonstrated that in patients with Anderson–Fabry disease resting regional blood flow is increased, not decreased as one would expect [25]. Cerebral circulation improved significantly by enzyme replacement therapy [26]. The decrease of blood flow velocities may signify a reduced risk of stroke in Anderson–Fabry disease. This hypothesis can be tested only after long-time experience with the drug.

2.2.5 Safety and tolerability

The cell culturing system where the product is produced was extensively tested. It was found to be free of viral and microbial contamination (EMEA report).

Single intravenous administration to rats and mice showed that treatment with agalsidase alfa was well-tolerated up to the highest doses given, 10 mg/kg in rats and 2.3 mg/kg in mice, 50 and 11 times the bi-weekly clinical dose, respectively. Intravenous dosing with agalsidase alfa caused no toxic effects in the 2-week dose finding study with rabbits (up to 1 mg/kg/day), in the 13-week studies with rats and Cynomolgus monkeys (up to 1 mg/kg/week) and in the 26-week study with rats. Mutagenicity studies were not performed. Formal carcinogenicity studies have also not been conducted with agalsidase alfa although the drug is intended for long-term treatment. However, carcinogenic potential is not anticipated based on the nature of the compound.

In patients, the enzyme agalsidase alfa is generally well-tolerated. In the controlled clinical trial, eight of the fourteen patients receiving the enzyme preparation had mild infusion reactions such as chills, facial flushing nausea or chest pain [21]. The reactions, that appeared ~ 45 min after the infusion, were easily controlled by treatment with antihistamines and

low-dose corticosteroids. Subsequently, the dosage of these drugs could be reduced without any further reactions. Enzyme replacement therapy could be continued. By the immunoprecipitation assay nine patients were positive with titres of approximately 1:10. The presence of antibodies did not correlate with the incidence of infusion reactions. IgE, IgA or IgM antibodies have not been detected in any patients.

2.2.6 Regulatory affairs

The drug Replagal® was approved in the EU and Norway in August 2001 and in New Zealand and Iceland in October 2001. In January 2002, the product received marketing approval in Israel, Switzerland and Czech Republic.

2.2.7 Conclusion

In summary, regular infusions of agalsidase alfa have been shown to be effective in reducing pain, improving kidney and heart function and in correcting brain circulation. The infusion reactions, that occur in ~ 10% of males under treatment, are tolerable and easy to manage with drugs such as paracetamol and/or antihistamines. All patients were able to continue the infusion, despite the infusion reactions.

3. Expert opinion

Anderson–Fabry disease is a complex disorder showing a wide clinical variation concerning the severity and the onset of symptoms. It has been shown that in individual cases, the clinical course cannot be predicted by the level of residual α -galactosidase activity or by analysing the underlying mutation. For these reasons, it is difficult to decide when enzyme replacement therapy should be initiated in asymptomatic patients. The decision becomes even more complicated as no surrogate markers that could reliably predict the progress of the disease currently exist. Plasma Gb₃ levels have been assumed to be a dependable marker, not only indicating the clinical severity but also being a useful tool to follow the effect of enzyme replacement therapy [27]. However, as vascular Gb₃ represents only a small proportion of total visceral Gb₃ storage, urinary Gb₃ levels seem to be a much more valuable marker, particularly regarding kidney function.

Anderson–Fabry disease has an immense influence on quality of life, reducing the median survival rate in both affected males and females [5,28]. Dialysis and/or kidney transplantation could not increase life expectancy, underlining the importance of extra-renal manifestation of this lysosomal storage disorder, such as cerebrovascular complications and cardiomyopathy. In many reports, agalsidase alfa has been clearly shown to have an effect on pain, heart dysfunction

and cerebrovascular manifestation, whereas in the agalsidase beta trial functional tests of the heart and the brain have not been performed [20]. In this study, a reduction of pain was observed in both patients who received the enzyme and in the placebo group.

IgG antibodies were detected in 55% of patients who had been treated with agalsidase alfa, whereas the incidence of antibody formation was higher (83%) in those who received agalsidase beta (data from the European labels of the products). Desnick reported on two patients whose agalsidase beta treatment had to be discontinued, as they developed IgE antibodies [29]. The higher incidence of allergic reactions associated with agalsidase beta may be explained by the differences in glycosylation that exist between both drugs and/or by the higher dosage that is applied in agalsidase beta.

Agalsidase alfa is produced in a cell culturing system using human cells, ensuring correct glycosylation of the protein, identical to that of the natural enzyme. This mode of manufacturing may explain why in the publications available as yet agalsidase alfa has been demonstrated to be more effective and safe in comparison with agalsidase beta, that is produced in animal (CHO) cells.

Regarding the application of agalsidase alfa, many questions still remain:

- What is the indication for enzyme replacement therapy in males (and females) with Anderson–Fabry disease? When should treatment be started? When there is heart and kidney dysfunction or in childhood to prevent later complications?
- Should every female with Anderson–Fabry disease receive the drug?
- Should young children be treated?
- What is the optimal dosage of agalsidase alfa? How often should the drug be given (every week? every month?)

Perhaps these questions can be answered within the next few years with increasing knowledge in Anderson–Fabry disease and when experience in enzyme replacement therapy has expanded.

The costs of enzyme replacement therapy are identical for both enzyme formulations (agalsidase alfa and agalsidase beta), taking into account the dosage recommended by the manufacturers. These costs are very high (~ € 150,000/year), however, they should be weighed against the expenditures caused by extensive resource utilisation and loss of productivity due to reduced lifespan. The costs of enzyme substitution may be reduced if alternative therapeutic options, such as galactose infusion [30], gene therapy [31] or substrate deprivation [32], become available.

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